Supporting Information

Total Synthesis and Biological Evaluation of Clavatadines C-E

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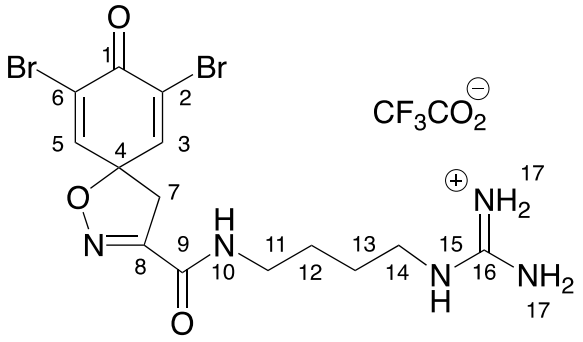
Table S1. Comparison of the Spectroscopic Data of Natural[1] vs. Synthetic Clavatadine C (**3**). The Numbering Scheme is Shown Below.

Clavatadine C (**3**)

Position	Natural **3**[a] DMSO-d_6 ^{13}C NMR 125 MHz δC	Synthetic **3**[c] DMSO-d_6 ^{13}C NMR 100 MHz δC	Natural **3**[d] DMSO-d_6 ^{1}H NMR 600 MHz δ_H, (*J* in Hz)	Synthetic **3**[e] DMSO-d_6 ^{1}H NMR 400 MHz δ_H, (*J* in Hz)
1	171.6, qC	171.6, qC		
2,6	121.6, qC	121.6, qC		
3,5	146.6, CH	146.7, CH	7.80 (s, 2H)	7.80 (s, 2H)
4	85.2, qC	85.2, qC		
7	43.1, CH_2	43.2, CH_2	3.55 (s, 2H)	3.55 (s, 2H)
8	155.0, qC	155.0, qC		
9	158.2, qC	158.2, qC		
10 (N)			8.63 (t, 1H)	8.66 (app. t, 5.6, 1H)
11	38.3, CH_2	38.3, CH_2	3.18 (dt, 6.0, 6.0, 2H)	3.18 (dt, 6.0, 5.6, 2H)
12	25.9, CH_2[b]	25.9, CH_2	1.49 (m, 2H)	1.54-1.42 (m, 2H)
13	26.0, CH_2[b]	26.0, CH_2	1.48 (m, 2H)	1.54-1.42 (m, 2H)
14	40.4, CH_2	40.4, CH_2	3.11 (dt, 6.0, 6.0, 2H)	3.10 (dt, 6.0, 5.6, 2H)
15 (N)			7.45 (m, 1H)	7.46 (app. t, 5.6, 1H)
16	156.6, qC	156.7, qC		
17"a (NH_2)			not listed	7.39-6.97 (v br s, 2H)[f]
17"b (NH_2)			not listed	6.97-6.54 (v br s, 2H)[f]

[a] Data taken from reference 6, Table 1, compound **1**. Not all carbon numbering in reference 6, Table 1, compound **1** matches the data. Correct carbon-peak correlations are presented here.
[b] Reference 6, Table 1 notes that the chemical shifts of these peaks are interchangeable.
[c] Data recorded using a concentrated sample of 30 mg in 0.75 mL of DMSO-d_6.
[d] Data taken from reference 6, Table 1, compound **1**.
[e] Data recorded using a dilute sample of 2 mg in 0.75 mL of DMSO-d_6.
[f] No copies of spectra, only data were published for the natural compound; therefore, the presence of these peaks in the natural spectrum can be inferred. The chemical shift range in the synthetic spectrum was estimated based on the boundary between these broad peaks.



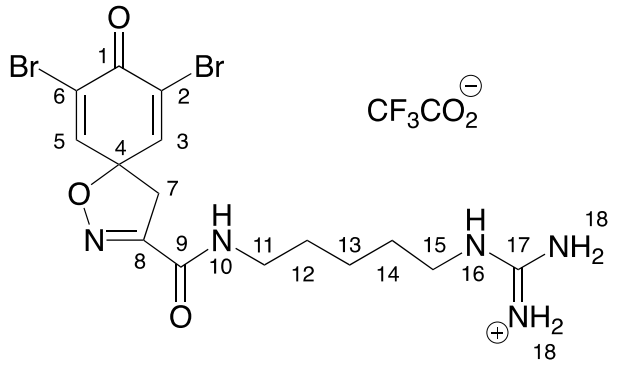
clavatadine C•HTFA (**3**•$\mathbf{CF_3CO_2H}$)

Table S2. Comparison of the Spectroscopic Data of Natural[1] vs. Synthetic Clavatadine D (**4**). The Numbering Scheme is Shown Below.

Clavatadine D (**4**)

Position	Natural **4**[a,b] DMSO-d_6 ^{13}C NMR 150 MHz δ_C	Synthetic **4**[c] DMSO-d_6 ^{13}C NMR 100 MHz δ_C	Natural **4**[d] DMSO-d_6 ^{1}H NMR 600 MHz δ_H, (*J* in Hz)	Synthetic **4**[f] DMSO-d_6 ^{1}H NMR 400 MHz δ_H, (*J* in Hz)
1	171.6, qC	171.6, qC		
2,6	121.5, qC	121.6, qC		
3,5	146.4, CH	146.7, CH	7.79 (s, 2H)	7.80 (s, 2H)
4	85.0, qC	85.1, qC		
7	42.9, CH_2	43.2, CH_2	3.55 (s, 2H)	3.55 (s, 2H)
8	154.8, qC	155.0, qC		
9	158.1, qC	158.1, qC		
10 (N)			8.59 (t, 1H)	8.61 (t, 6.0, 1H)
11	38.5, CH_2	38.6, CH_2	3.16 (dt, 6.0, 6.0, 2H)	3.16 (dt, 6.0, 5.6, 2H)
12	28.2, CH_2	28.4, CH_2	1.49 (tt, 6.0, 6.0, 2H)[e]	1.53-1.43 (m, 2H)
13	23.2, CH_2	23.4, CH_2	1.29 (tt, 6.0, 6.0, 2H)	1.33-1.23 (m, 2H)
14	27.9, CH_2	28.1, CH_2	1.48 (tt, 6.0, 6.0, 2H)[e]	1.53-1.43 (m, 2H)
15	40.4, CH_2	40.7, CH_2	3.08 (dt, 6.0, 6.0, 2H)	3.08 (dt, 6.0, 5.6, 2H)
16 (N)			7.41 (br t, 6.0, 1H)	7.39 (app. t, 5.6, 1H)
17	156.5, qC	156.7, qC		
18"a (NH_2)			not listed	7.39-6.97 (v br s, 2H)[g]
18"b (NH_2)			not listed	6.97-6.54 (v br s, 2H)[g]

[a] Data taken from reference 6, Table 1, compound **2**. Not all carbon numbering in reference 6, Table 1, compound **1** matches the data. Correct carbon-peak correlations are presented here.
[b] Reference 6, Table 1 notes that these chemical shifts were determined by 2D NMR experiments (^{13}C, 150 MHz).
[c] Data recorded using a concentrated sample of 15 mg in 0.75 mL of DMSO-d_6.
[d] Data taken from reference 6, Table 1, compound **2**.
[e] Reference 6, Table 1 notes that the chemical shifts of these peaks are interchangeable.
[f] Data recorded using a dilute sample of 2 mg in 0.75 mL of DMSO-d_6.
[g] No copies of spectra, only data were published for the natural compound; therefore, the presence of these peaks in the natural spectrum can be inferred. The chemical shift range in the synthetic spectrum was estimated based on the boundary between these broad peaks.



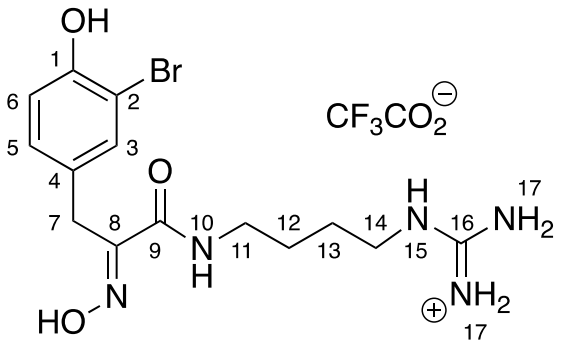
clavatadine D•HTFA (**4•CF_3CO_2H**)

Table S3. Comparison of the Spectroscopic Data of Natural[1] vs. Synthetic Clavatadine E (**5**). The Numbering Scheme is Shown Below.

Clavatadine E (**5**)

Position	Natural **5**[a,b] DMSO-d_6 ^{13}C NMR 150 MHz δ_C	Synthetic **5**[c] DMSO-d_6 ^{13}C NMR 100 MHz δ_C	Natural **5**[d] DMSO-d_6 ^{1}H NMR 600 MHz δ_H, (J in Hz)	Synthetic **5**[e] DMSO-d_6 ^{1}H NMR 400 MHz δ_H, (J in Hz)
1	152.2, qC	152.4, qC		
2	108.7, qC	108.8, qC		
3	132.4, CH	132.7, CH	7.28 (d, 1.8, 1H)	7.28 (d, 2.0, 1H)
4	128.8, qC	128.8, qC		
5	128.8, CH	129.1, CH	7.01 (dd, 8.4, 1.8, 1H)	7.01 (dd, 8.4, 2.0, 1H)
6	115.9, CH	116.1, CH	6.83 (d, 8.4, 1H)	6.83 (d, 8.4, 1H)
7	27.5, CH_2	27.7, CH_2	3.69 (s, 2H)	3.69 (s, 2H)
8	152.0, qC	152.1, qC		
9	163.0, qC	163.2, qC		
1-OH			10.02 (s, 1H)	10.04 (s, 1H)
N-OH			11.75 (s, 1H)	11.76 (s, 1H)
10 (N)			7.99 (t, 6.0, 1H)	8.02 (t, 6.0, 1H)
11	37.9, CH_2	38.2, CH_2	3.15 (dt, 6.0, 6.0, 2H)	3.13 (dt, 7.2, 6.0, 2H)
12	25.8, CH_2	26.3, CH_2	1.43 (m, 2H)	1.43 (m, 4H)
13	25.8, CH_2	26.0, CH_2	1.42 (m, 2H)	combined with H12
14	39.9, CH_2	40.4, CH_2	3.08 (dt, 6.0, 6.0, 2H)	3.08 (dt, 7.2, 5.6, 2H)
15 (N)			7.39 (t, 6.0, 1H)	7.41 (t, 5.6, 1H)
16	156.5, qC	156.7, qC		
17" (NH_2)			not listed	7.6-6.8 (v br, 4H)[f]

[a] Data taken from reference 6, Table 2, compound **3.** Not all carbon numbering in reference 6, Table 2, compound **3** matches the data. Correct carbon-peak correlations are presented here.
[b] Reference 6, Table 1 notes that these chemical shifts were determined by 2D NMR experiments (^{13}C, 150 MHz).
[c] Data recorded using a concentrated sample of 25 mg in 0.75 mL of DMSO-d_6.
[d] Data taken from reference 6, Table 2, compound **3.**
[e] Data recorded using a dilute sample of 2 mg in 0.75 mL of DMSO-d_6.
[f] No copies of spectra, only data were published for the natural compound; therefore, the presence of these peaks in the natural spectrum can be inferred. The chemical shift in the synthetic spectrum was estimated because they overlap with other peaks in this range.



clavatadine E•HTFA (**5•CF_3CO_2H**)

Table S4. NCI-60 one-dose assay for synthetic clavatadine C (**3**)

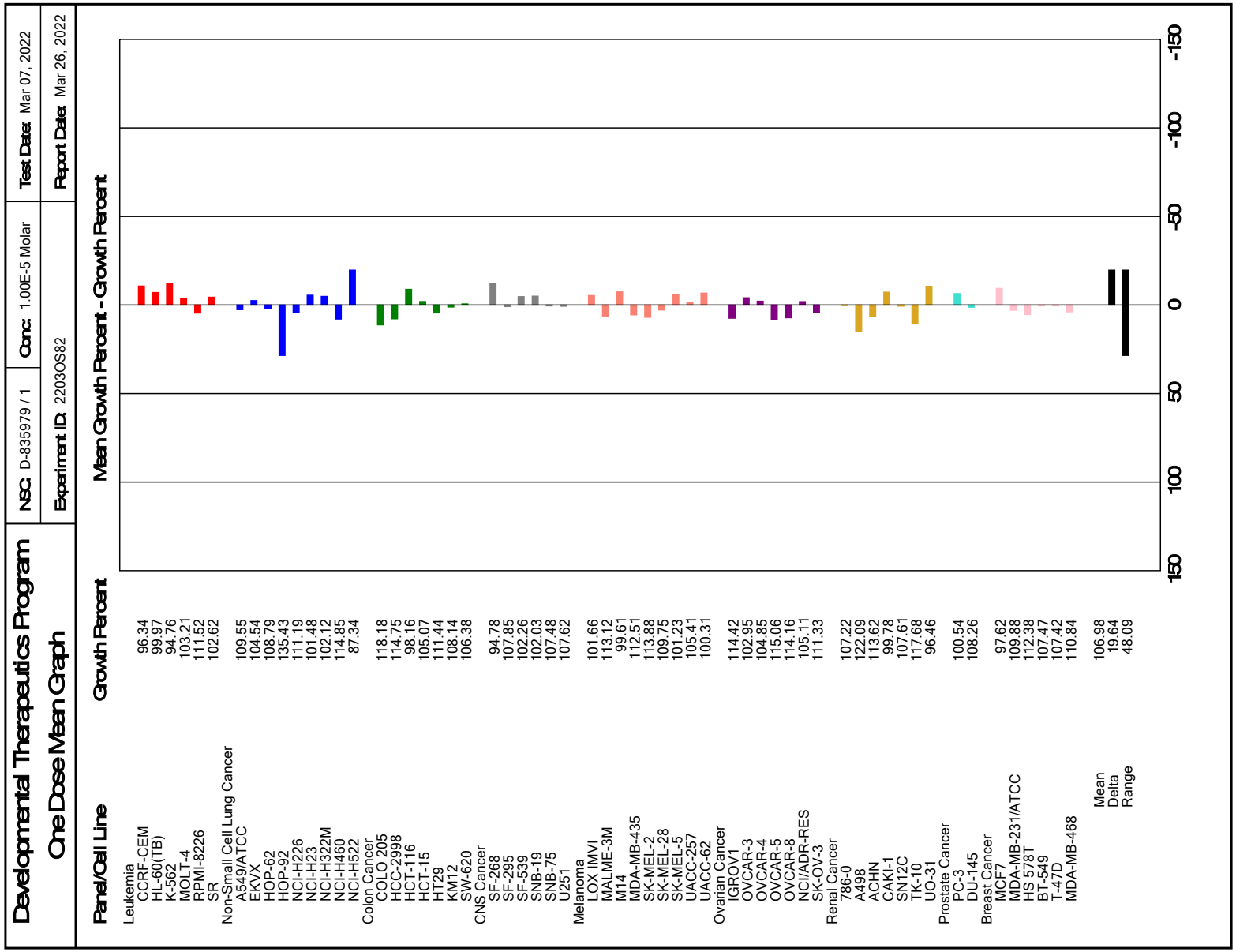


Table S5. NCI-60 one-dose assay for synthetic clavatadine D (**4**)

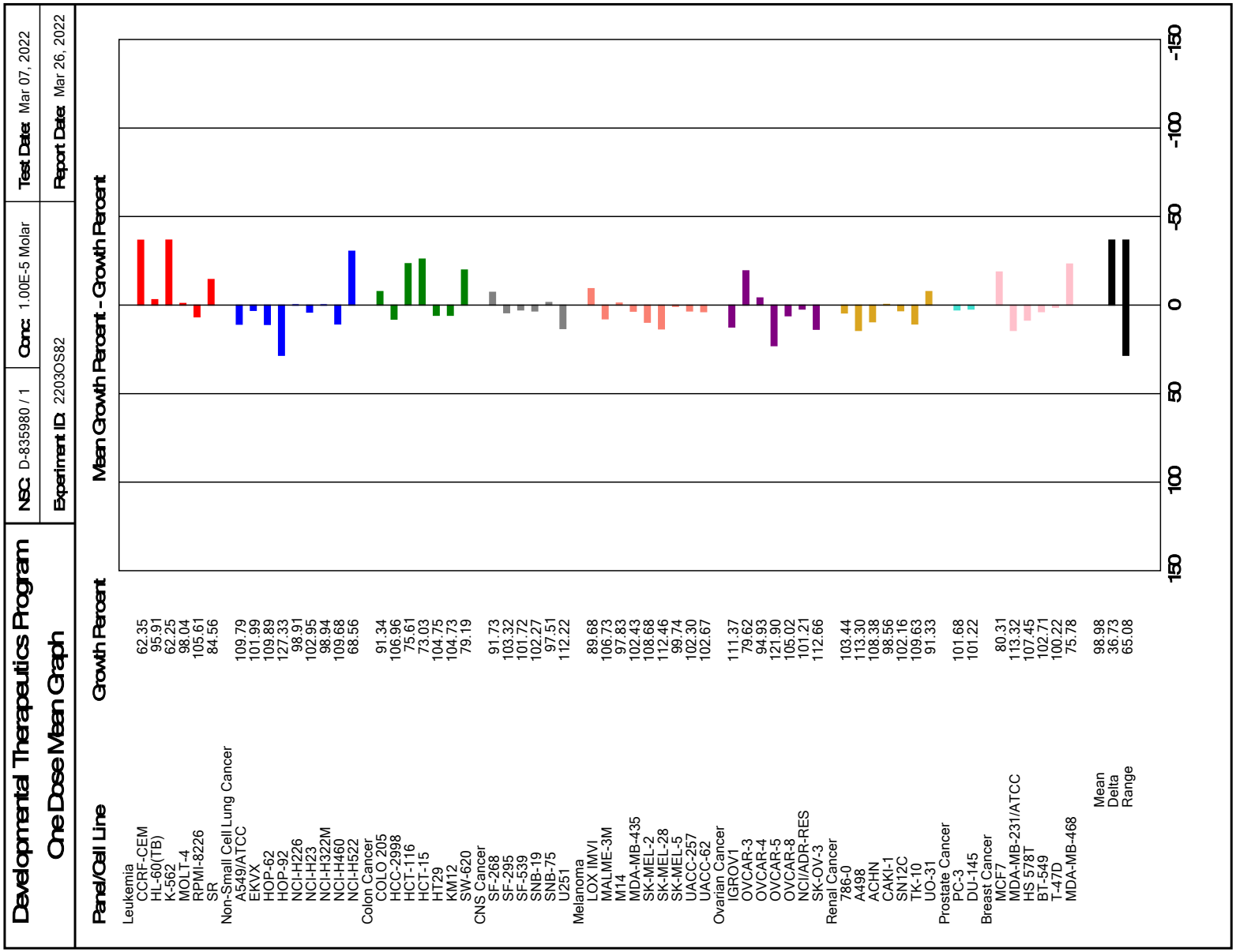
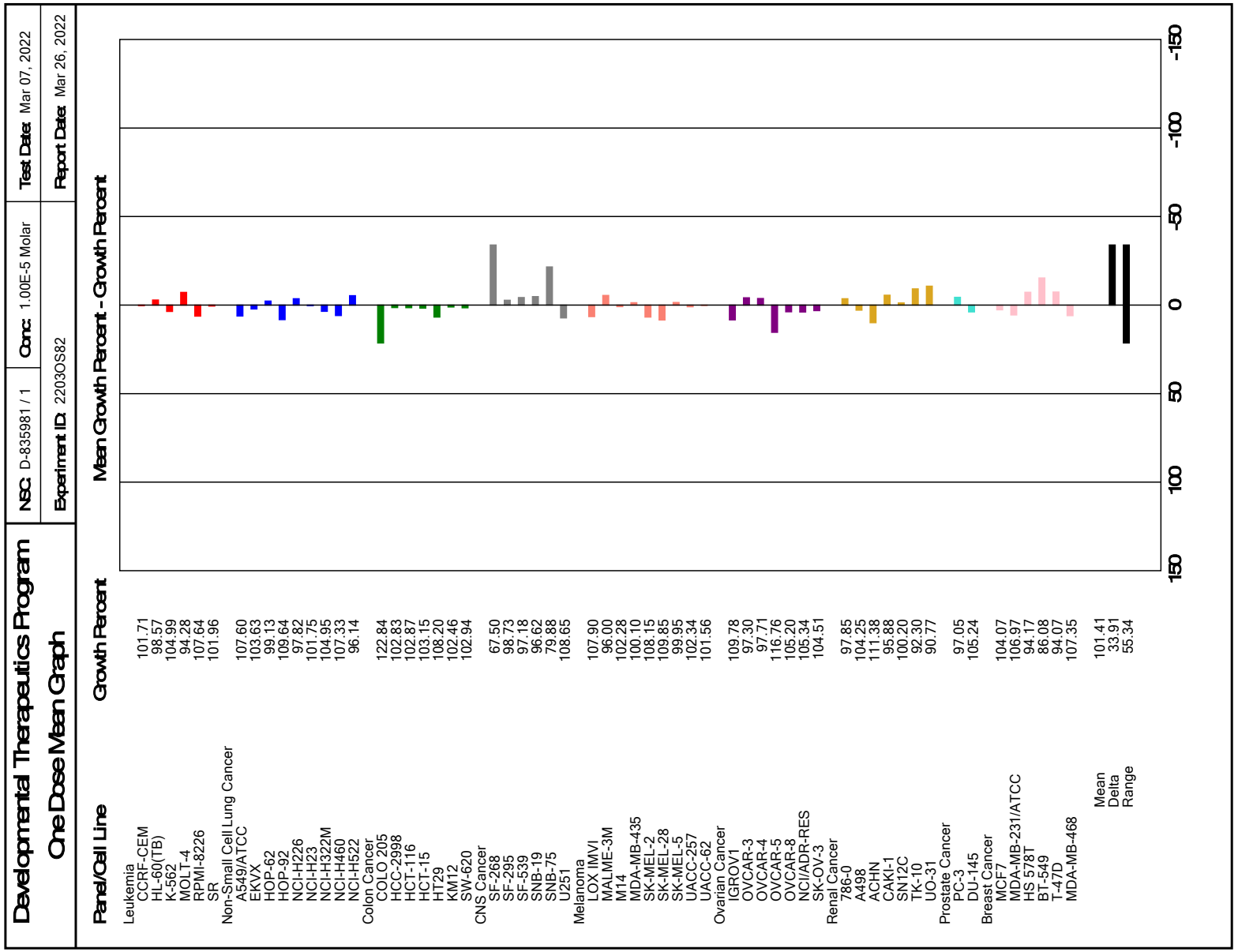


Table S6. NCI-60 one-dose assay for synthetic clavatadine E (**5**)



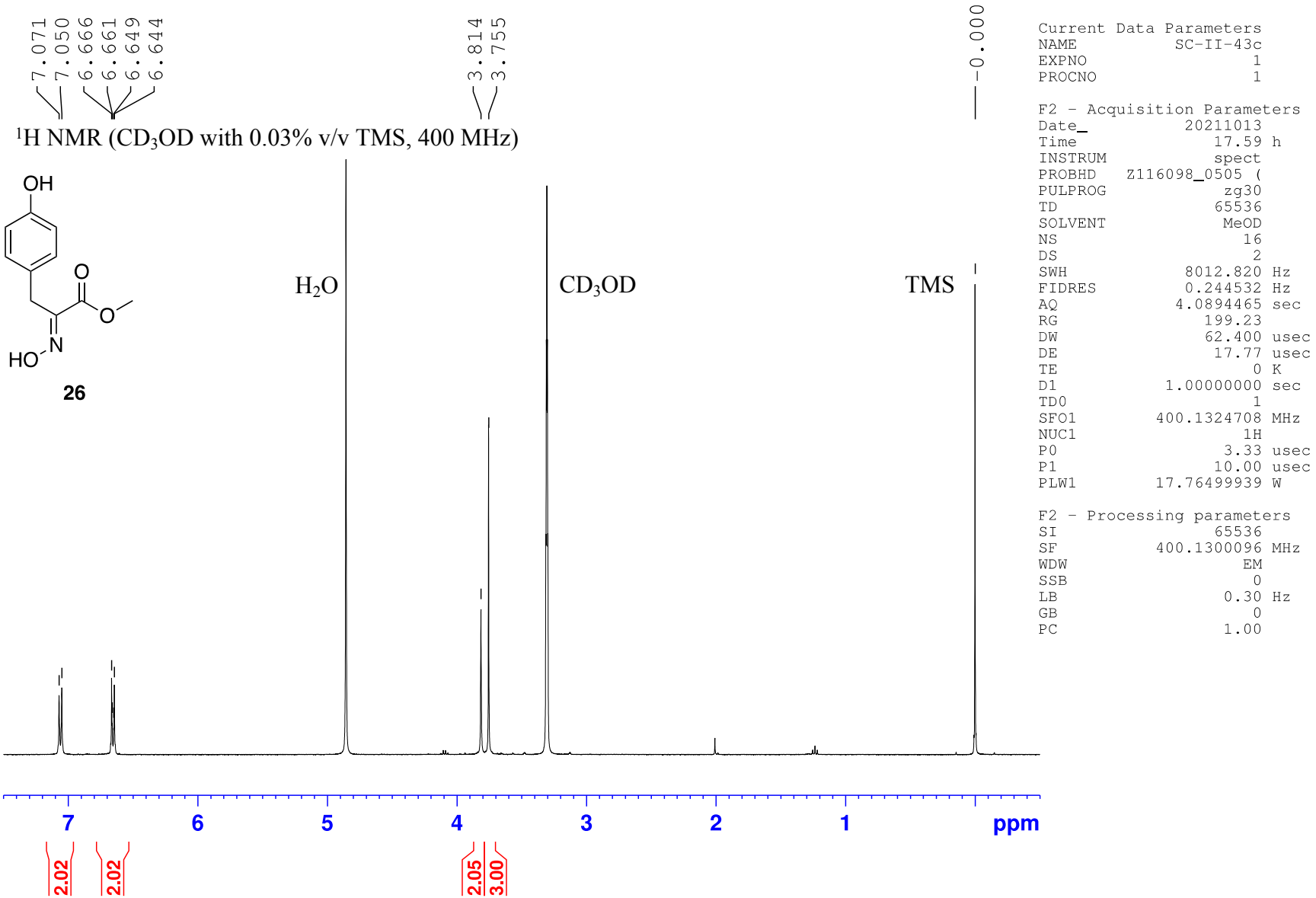


Figure S1. ^{1}H NMR (400 MHz, CD_3OD) spectrum of the known compound **26.**

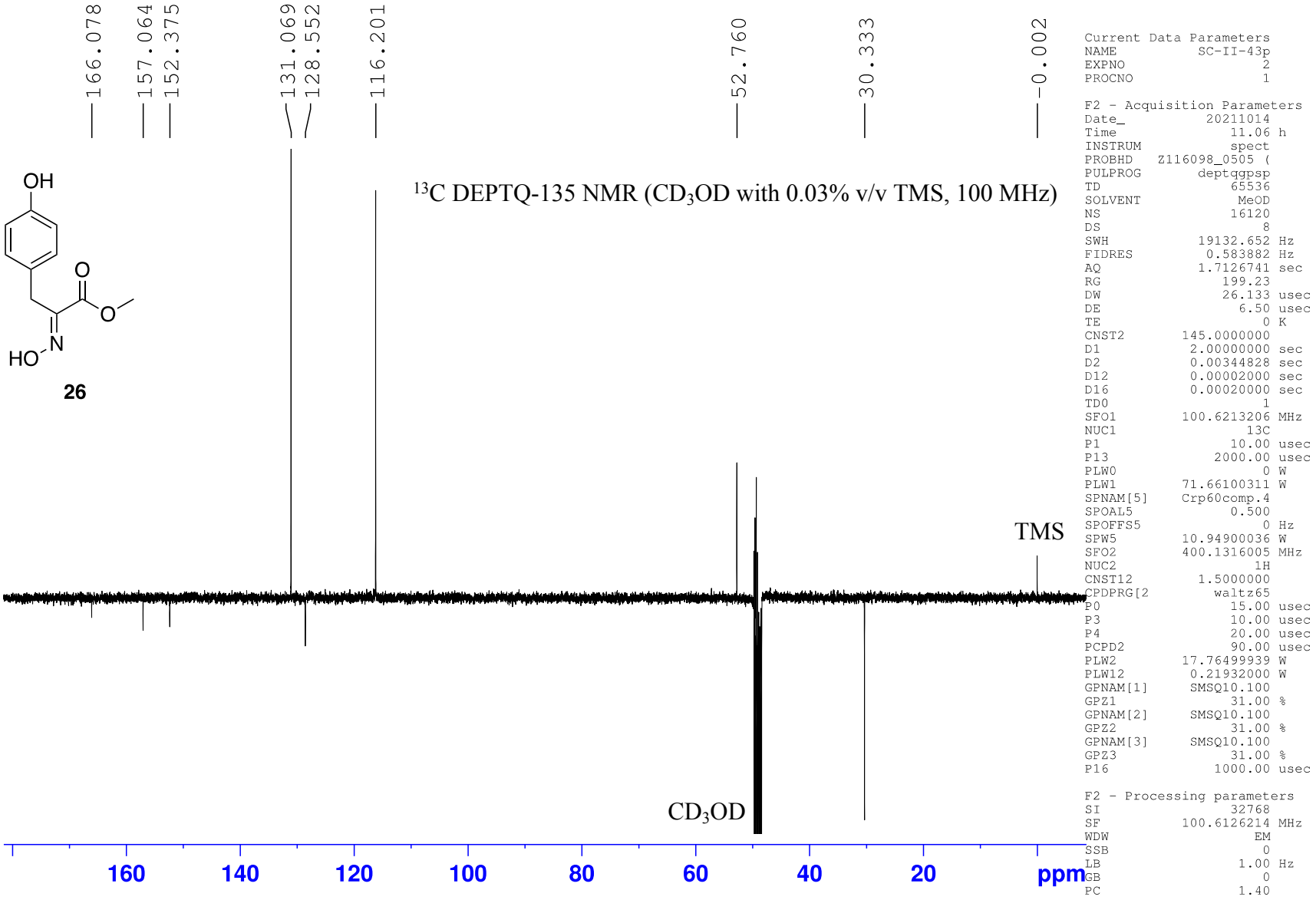


Figure S2. ^{13}C DEPTQ-135 NMR (100 MHz, CD_3OD) spectrum of the known compound **26.**

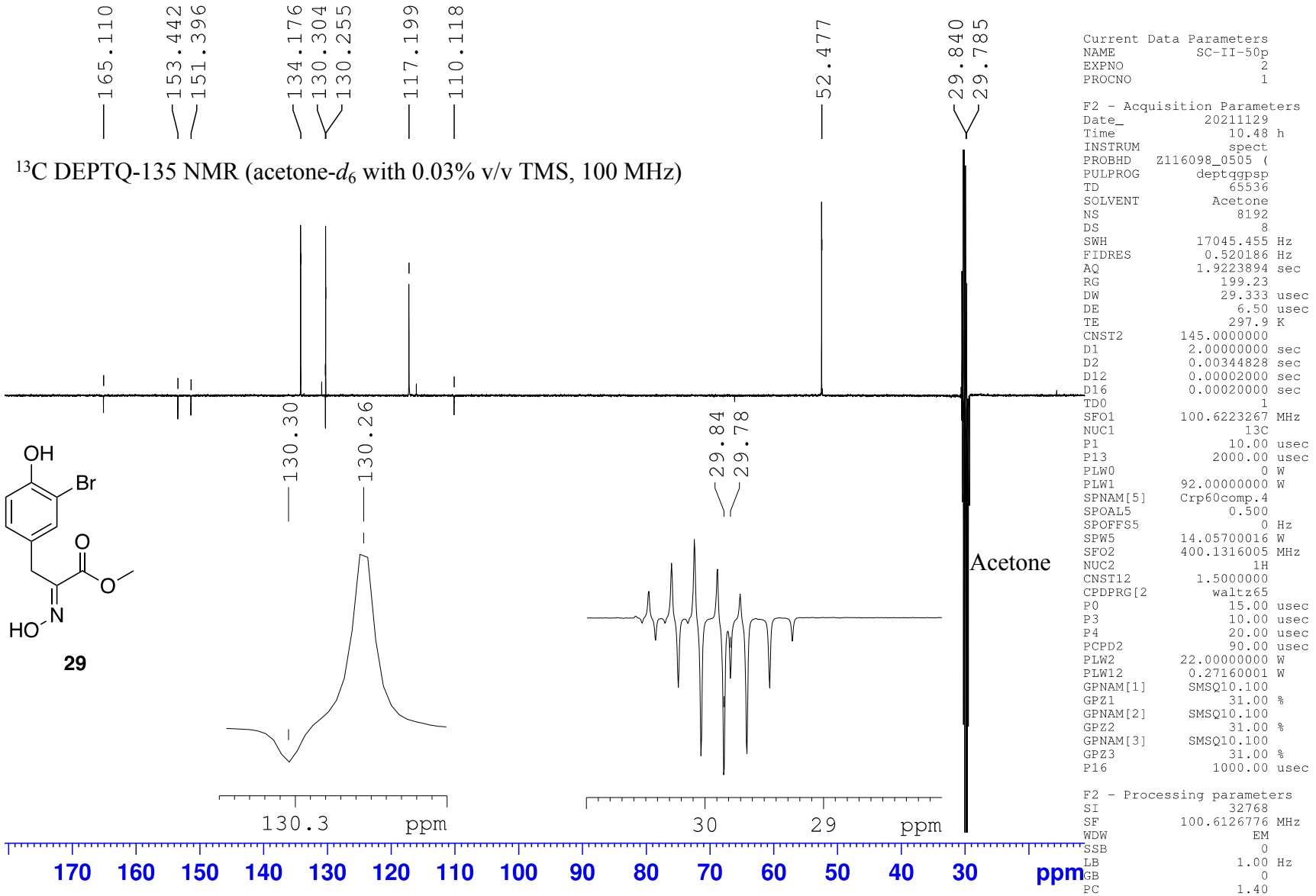
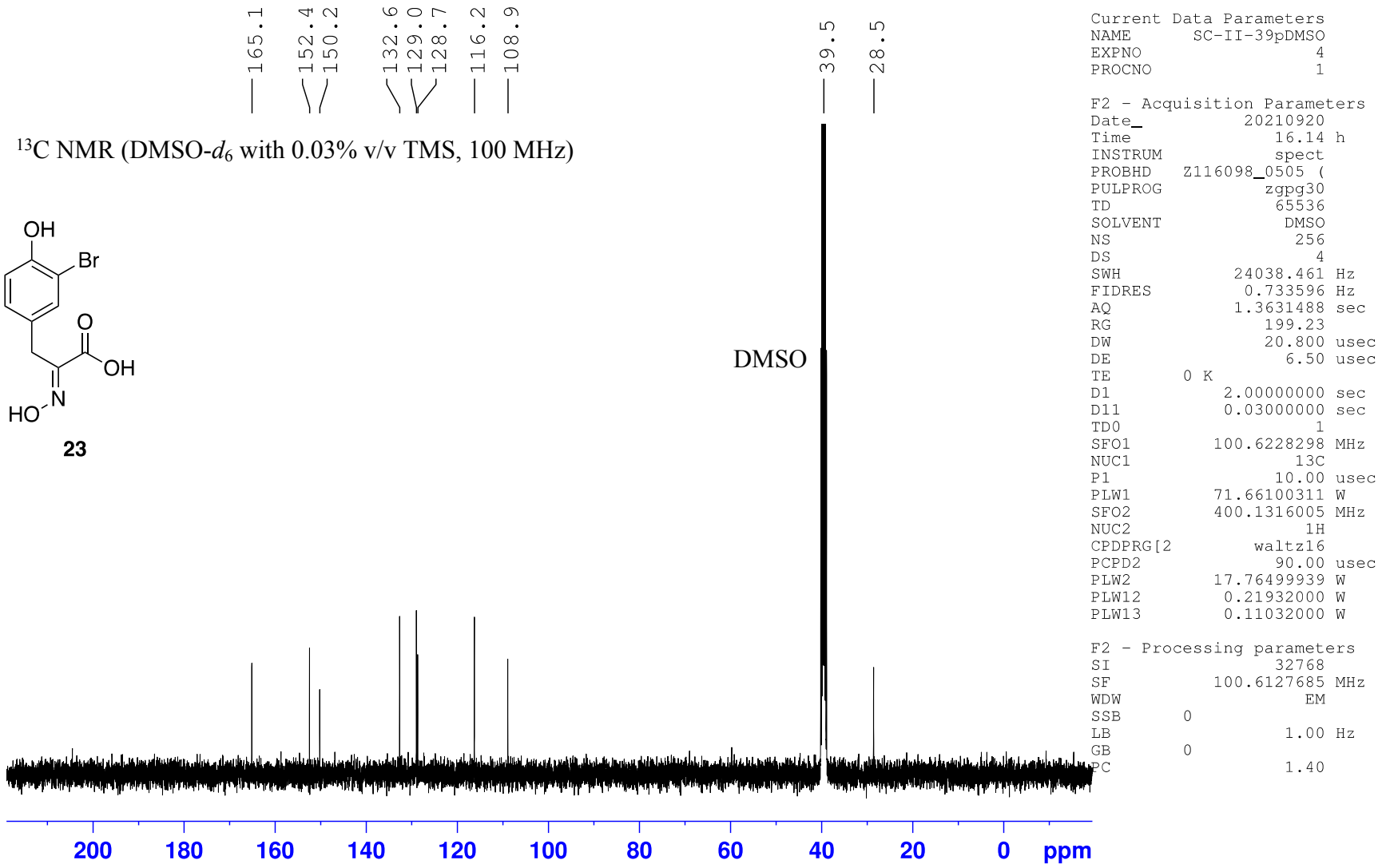


Figure S3. ^{13}C DEPTQ-135 NMR (100 MHz, acetone-d_6) spectrum of the known compound **29**.



^{13}C NMR (DMSO-d_6 with 0.03% v/v TMS, 100 MHz)

23

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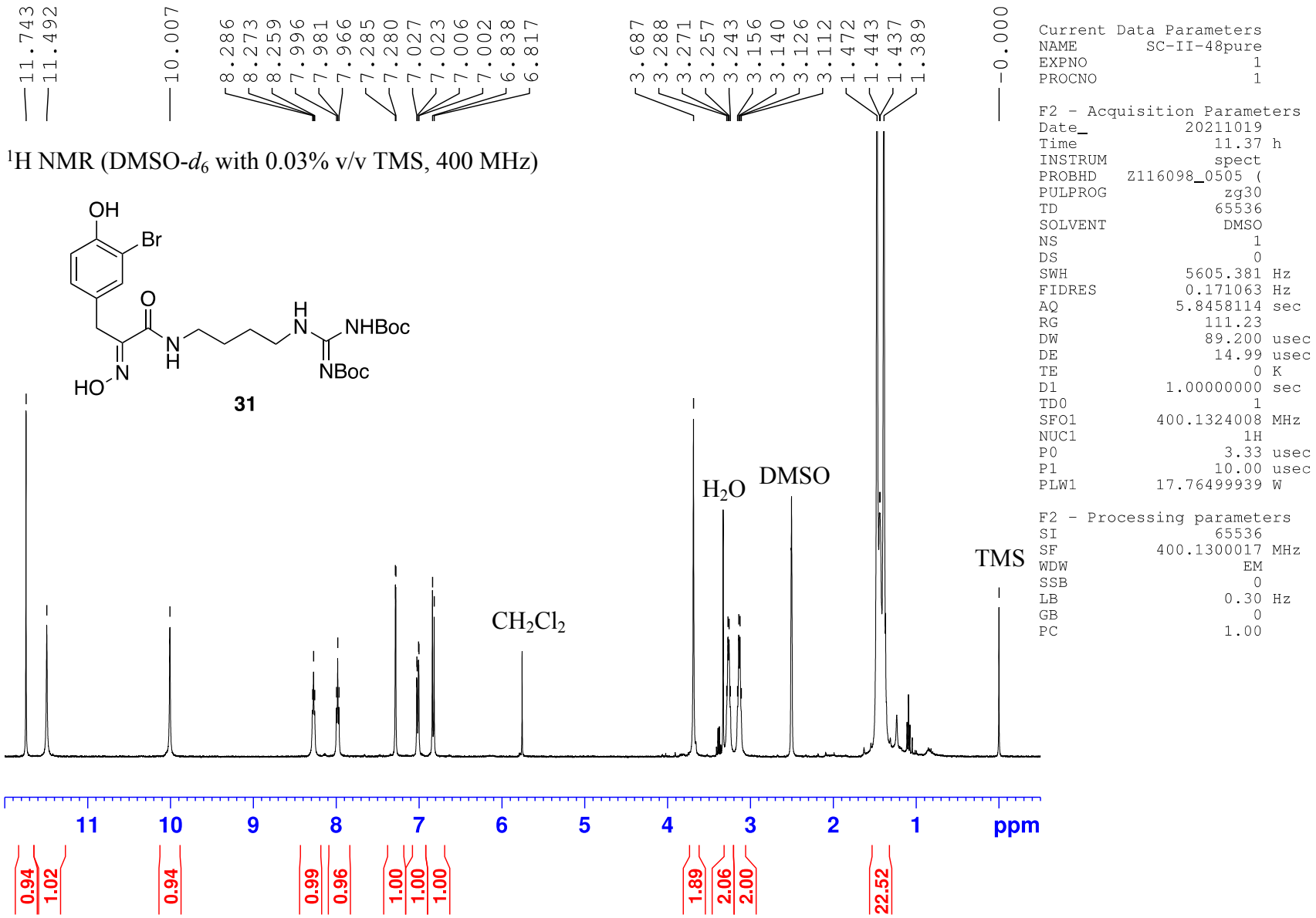


Figure S5. ^{1}H NMR (400 MHz, DMSO-d_6) spectrum of the new compound **31**.

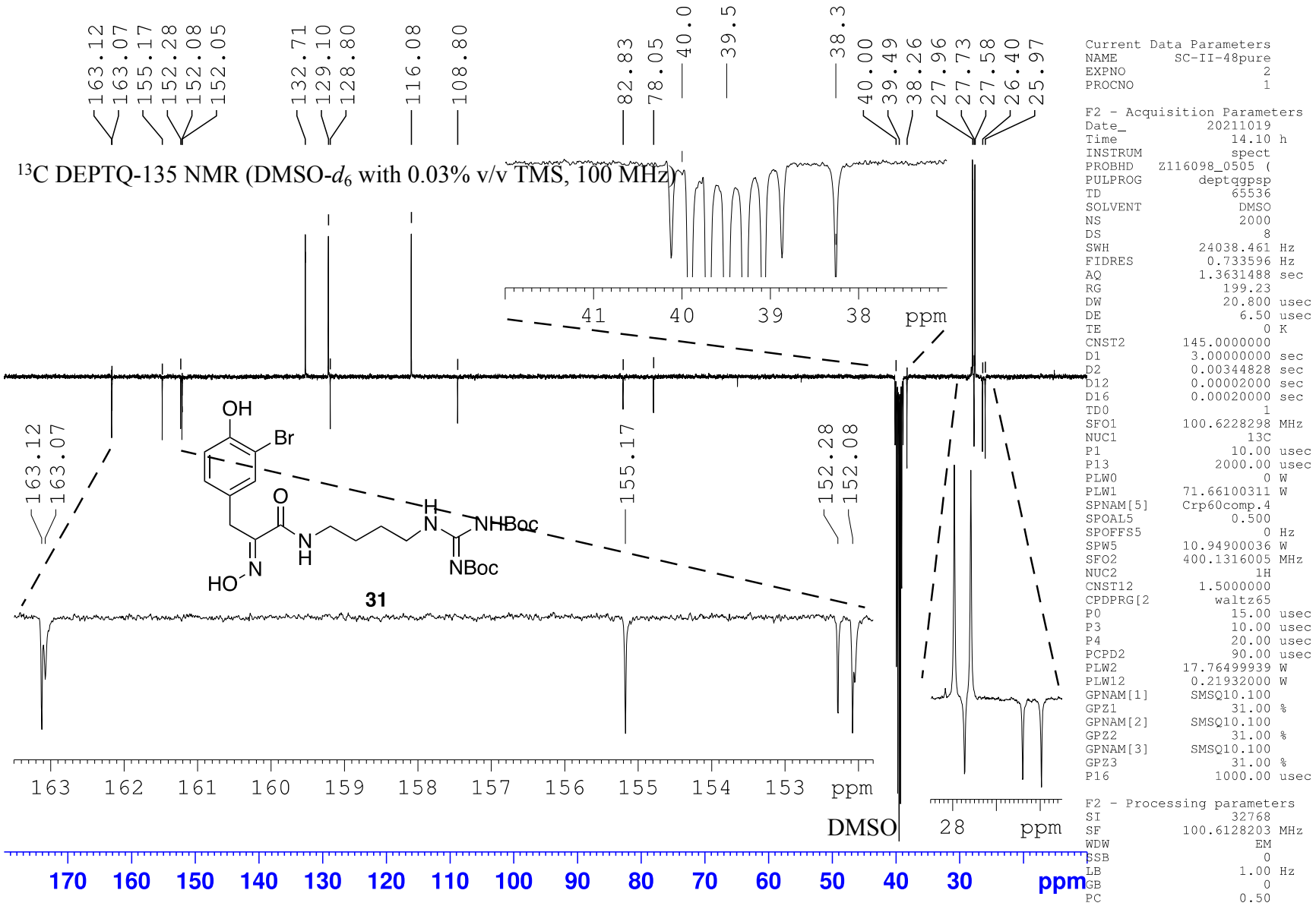


Figure S6. ^{13}C DEPTQ-135 NMR (100 MHz, DMSO-d_6) spectrum of the new compound **31**.

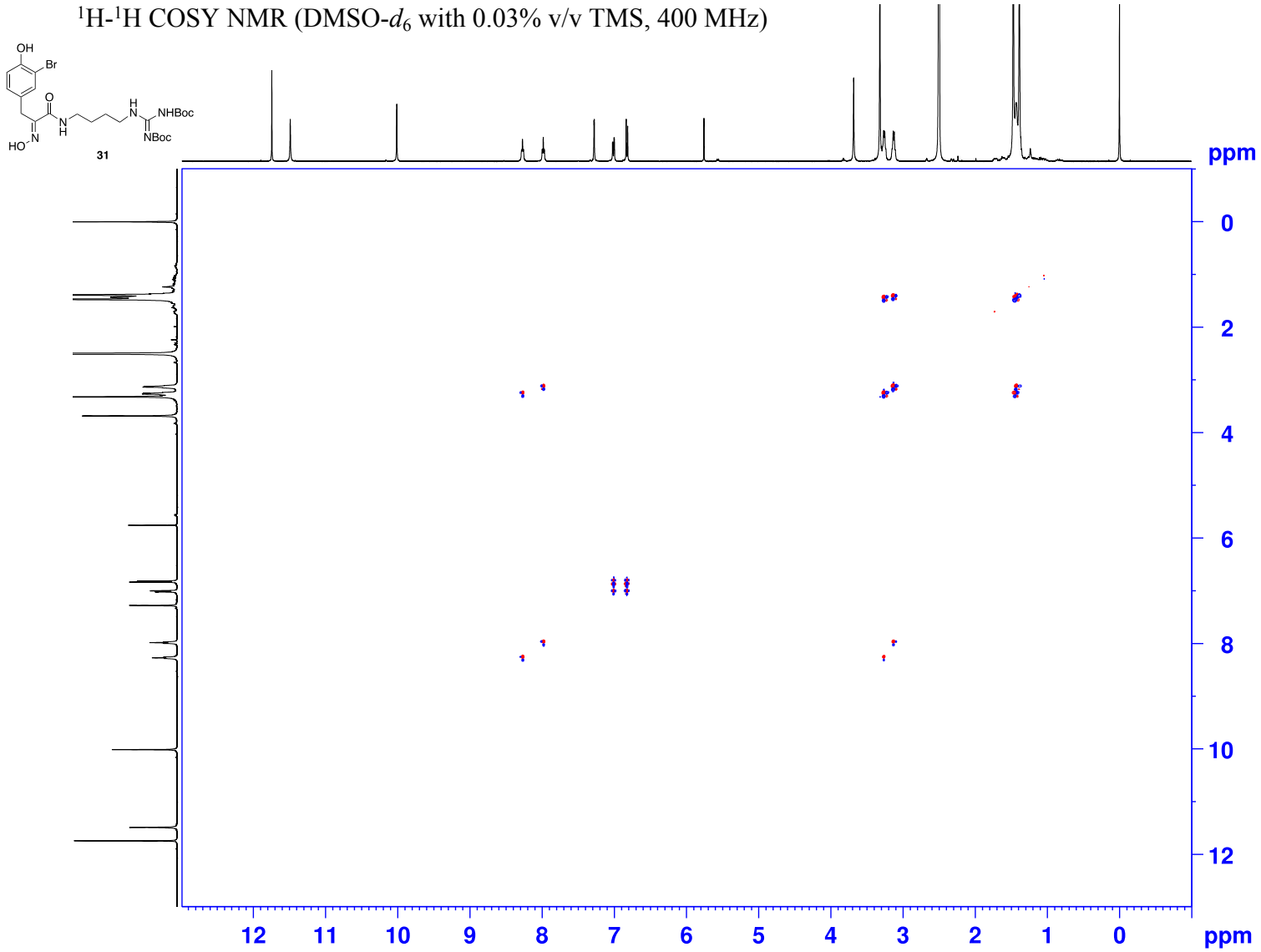


Figure S7. ^{1}H-^{1}H COSY NMR (400 MHz, DMSO-d_6) spectrum of the new compound **31**.

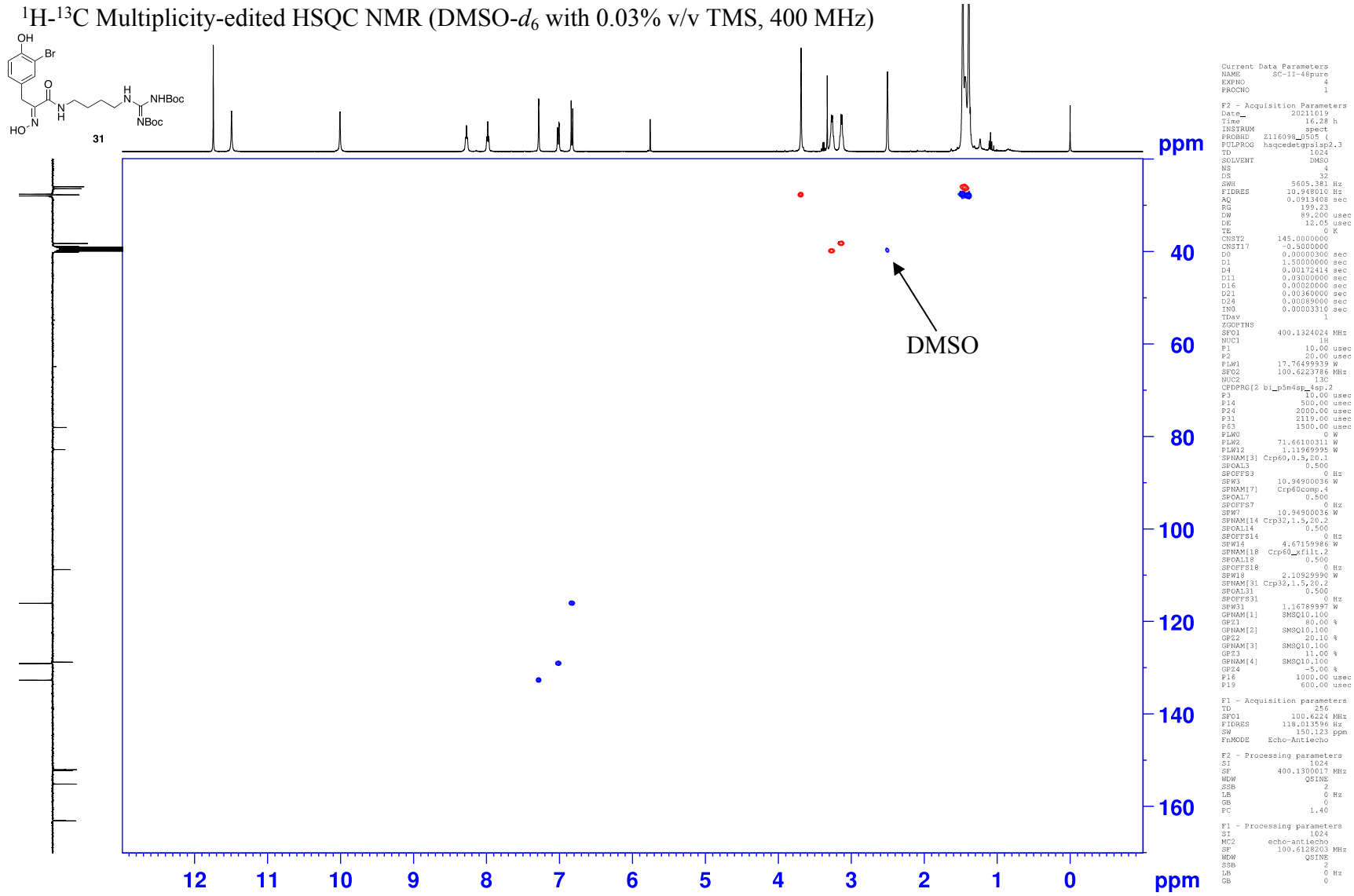
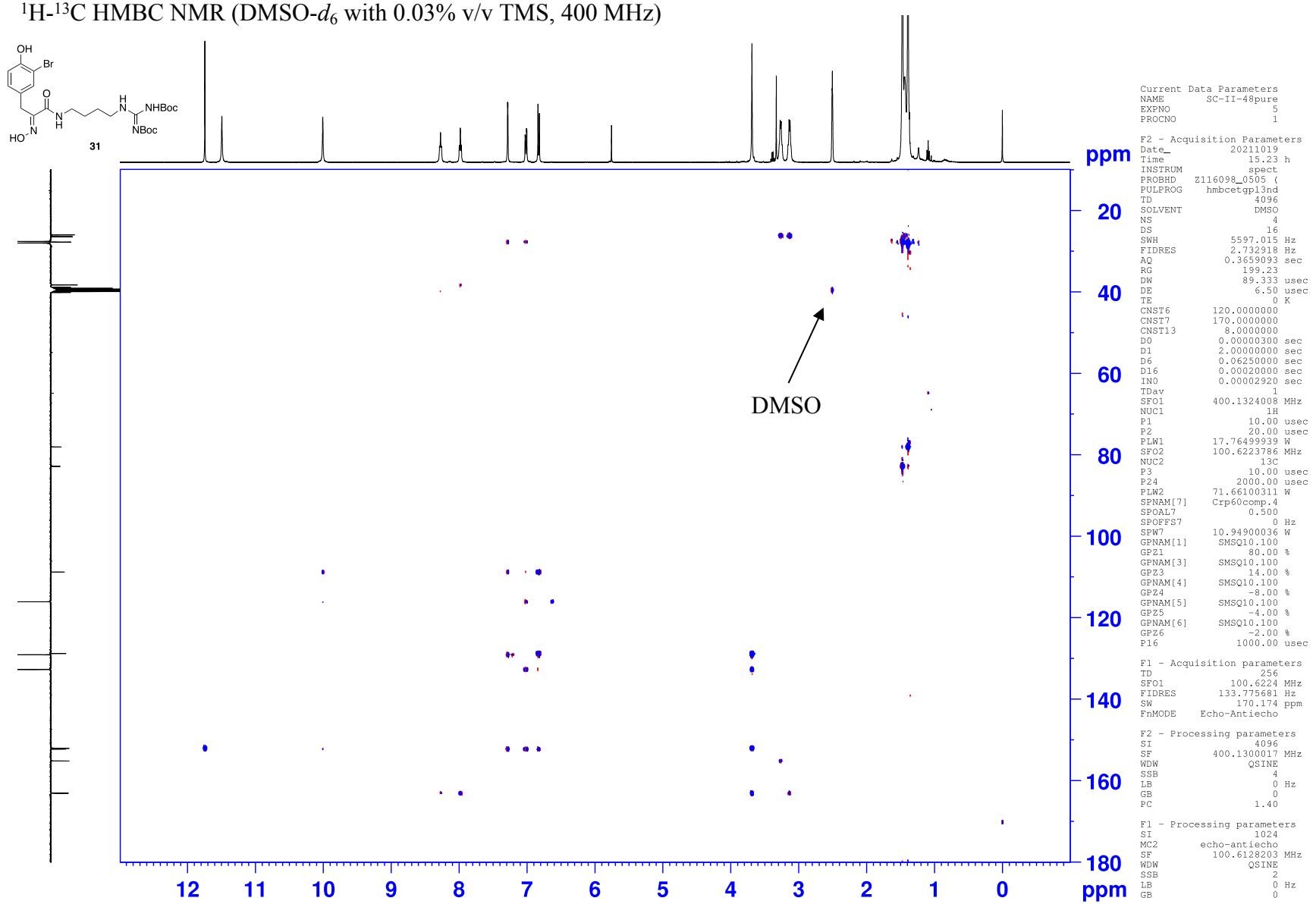


Figure S8. ^{1}H-^{13}C Multiplicity Edited HSQC NMR (400 MHz, DMSO-d_6) spectrum of the new compound **31**.

^{1}H-^{13}C HMBC NMR (DMSO-d_6 with 0.03% v/v TMS, 400 MHz)

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SW               170.174 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
SI                 4096
SF           400.1300017 MHz
WDW                QSINE
SSB                    4
LB                     0 Hz
GB                     0
PC                  1.40

F1 - Processing parameters
SI                 1024
MC2        echo-antiecho
SF           100.6128203 MHz
WDW                QSINE
SSB                    2
LB                     0 Hz
GB                     0
```

Figure S9. ^{1}H-^{13}C HMBC NMR (400 MHz, DMSO-d_6) spectrum of the new compound **31**.

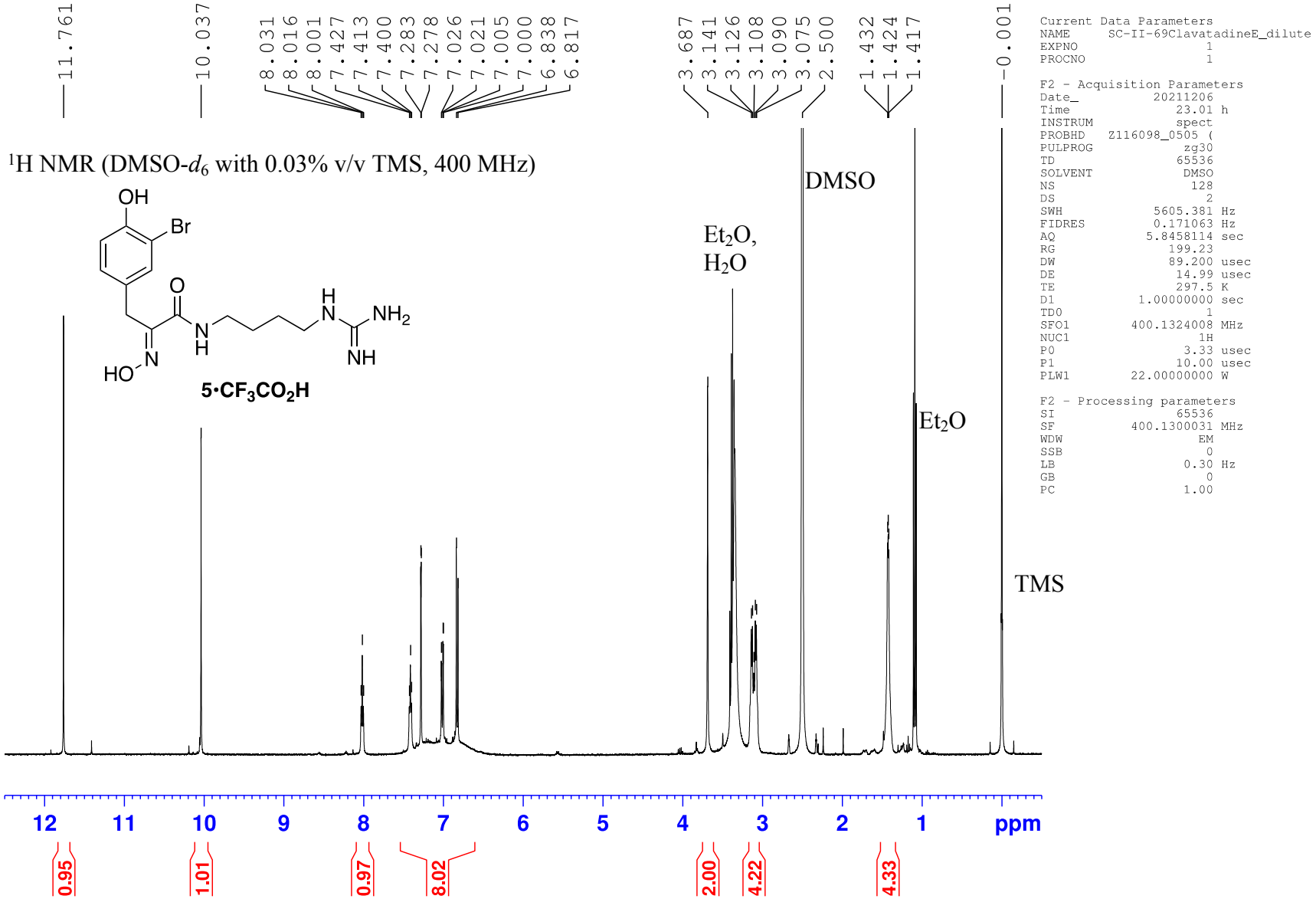
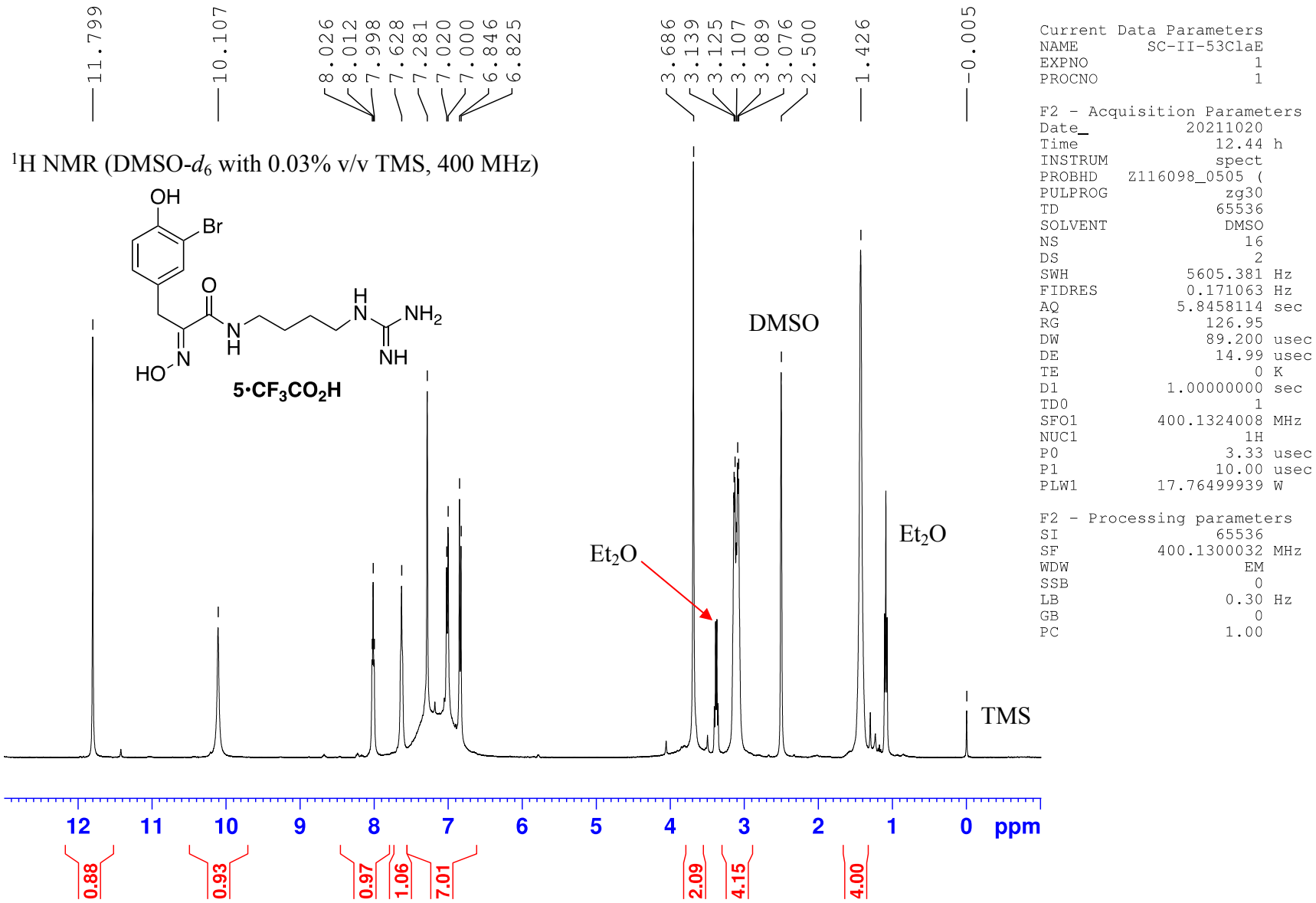


Figure S10. ^{1}H NMR (400 MHz, DMSO-d_6) spectrum of dilute, unpurified, synthetic clavatadine E (**5**).

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Current Data Parameters
NAME        SC-II-53ClaE
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20211020
Time              12.44 h
INSTRUM            spect
PROBHD    Z116098_0505 (
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                    16
DS                     2
SWH             5605.381 Hz
FIDRES          0.171063 Hz
AQ              5.8458114 sec
RG                126.95
DW                89.200 usec
DE                14.99 usec
TE                    0 K
D1           1.00000000 sec
TD0                    1
SFO1        400.1324008 MHz
NUC1                  1H
P0                 3.33 usec
P1                10.00 usec
PLW1        17.76499939 W

F2 - Processing parameters
SI                 65536
SF          400.1300032 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
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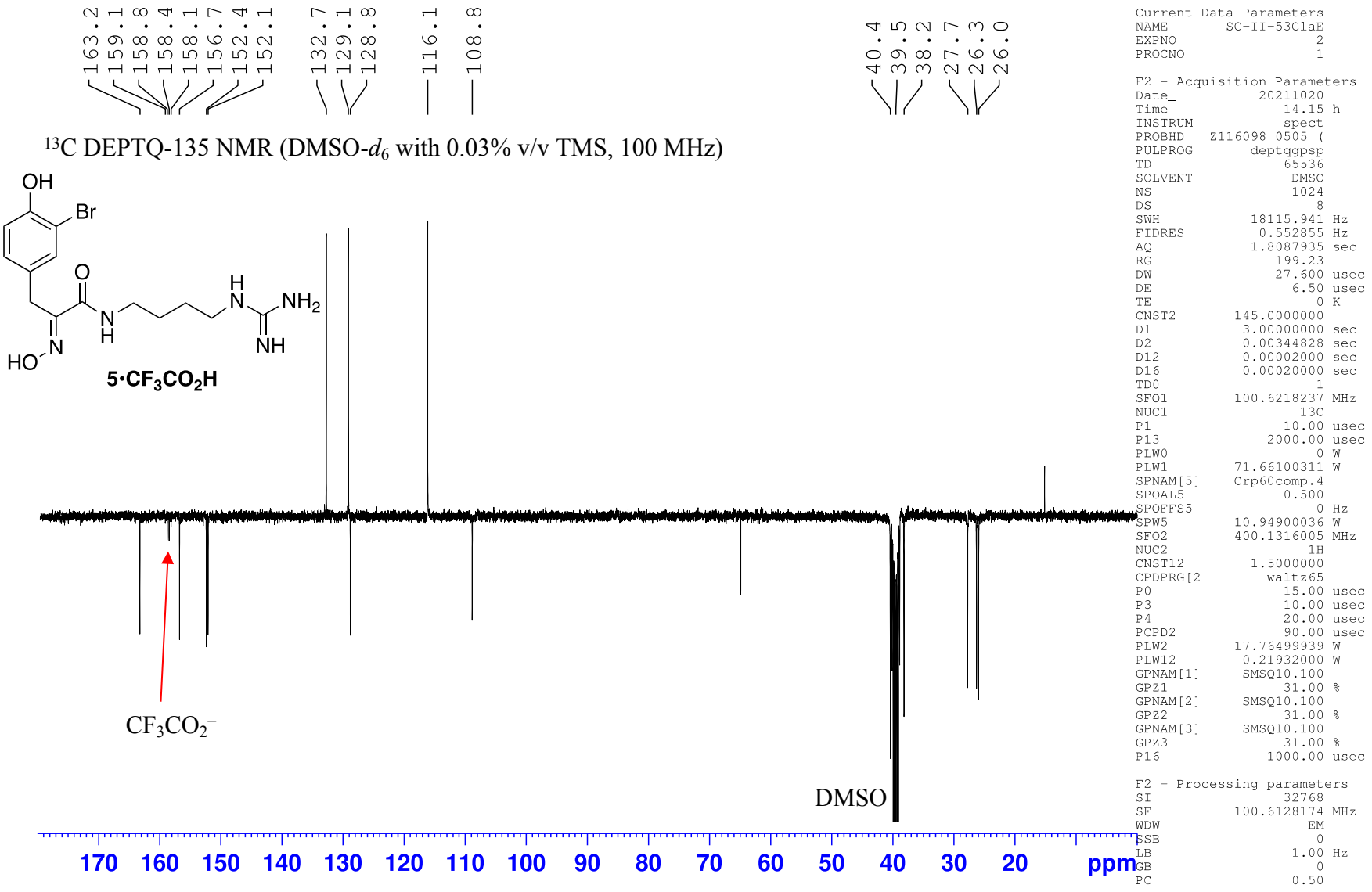
Figure S11. ^{1}H NMR (400 MHz, DMSO-d_6) spectrum of concentrated, unpurified, synthetic clavatadine E (**5**).



^{13}C DEPTQ-135 NMR (DMSO-d_6 with 0.03% v/v TMS, 100 MHz)

Figure S12. ^{13}C DEPTQ-135 NMR (100 MHz, DMSO-d_6) spectrum of unpurified, synthetic clavatadine E (**5**).

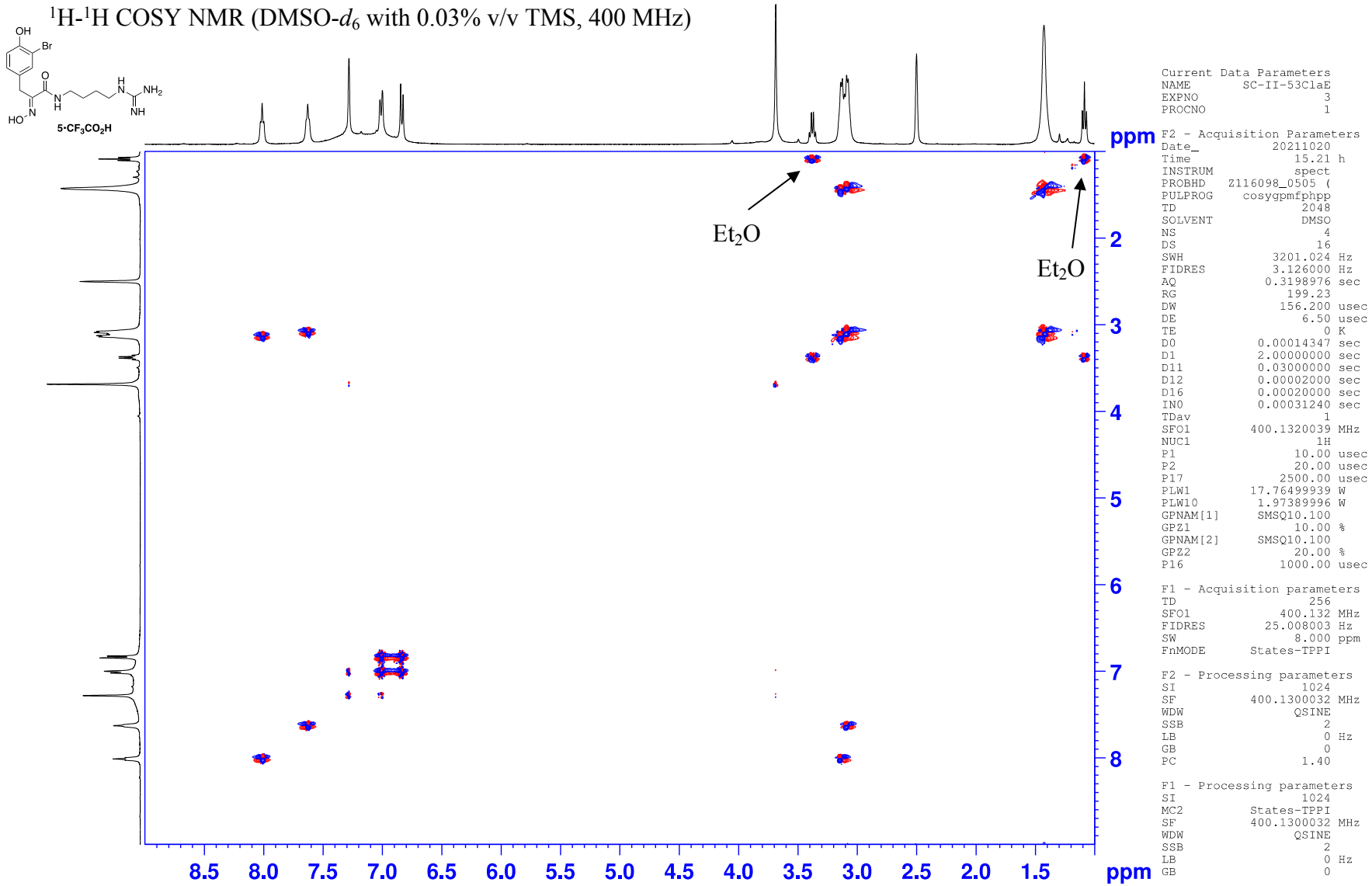


Figure S13. ^{1}H-^{1}H COSY NMR (400 MHz, DMSO-d_6) spectrum of unpurified, synthetic clavatadine E (**5**).

^{1}H-^{13}C Multiplicity-edited HSQC NMR (DMSO-d_6 with 0.03% v/v TMS, 400 MHz)

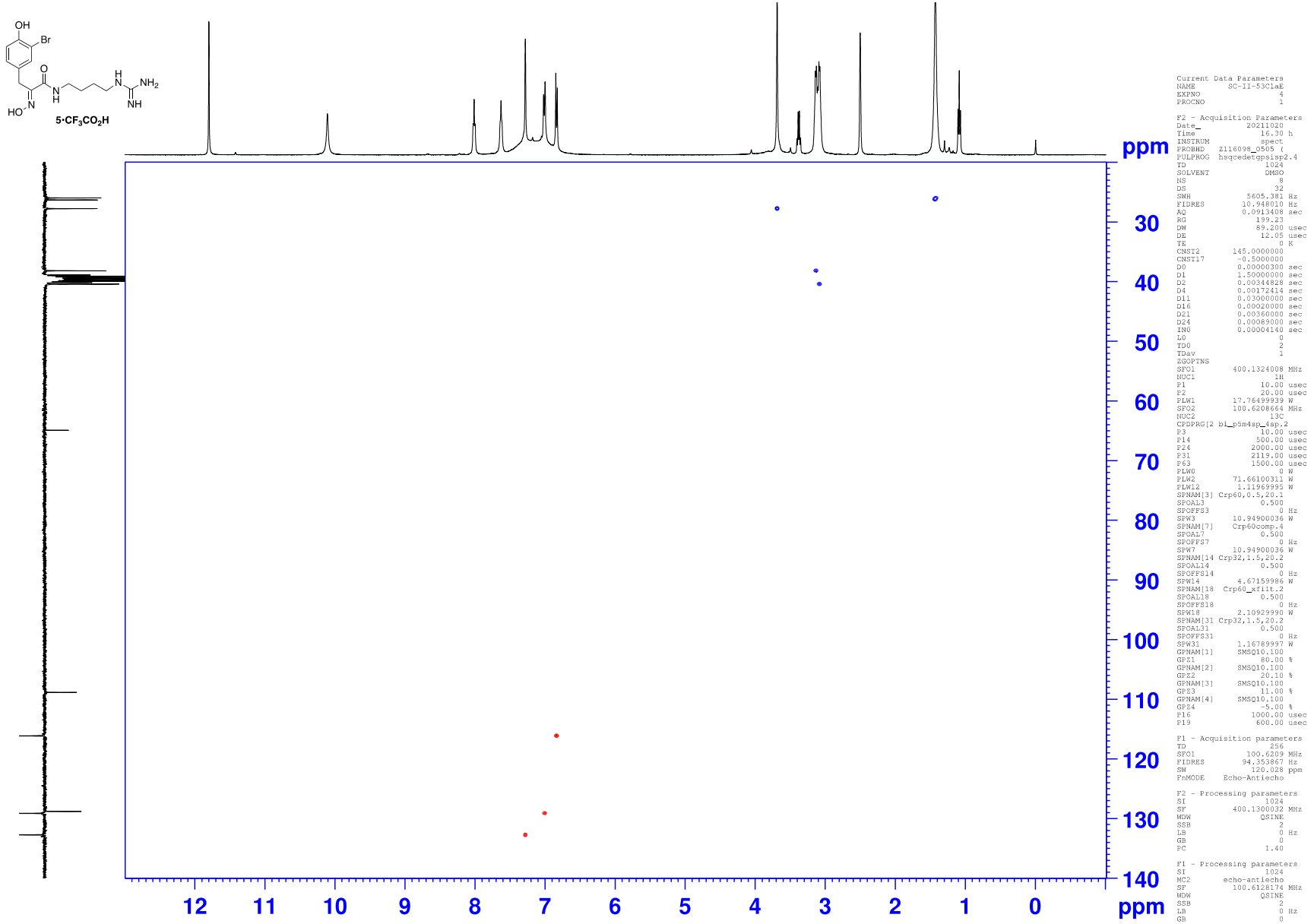


Figure S14. ^{1}H-^{13}C Multiplicity Edited HSQC NMR (400 MHz, DMSO-d_6) spectrum of unpurified, synthetic clavatadine E (**5**).

^{1}H-^{13}C HMBC NMR (DMSO-d_6 with 0.03% v/v TMS, 400 MHz)

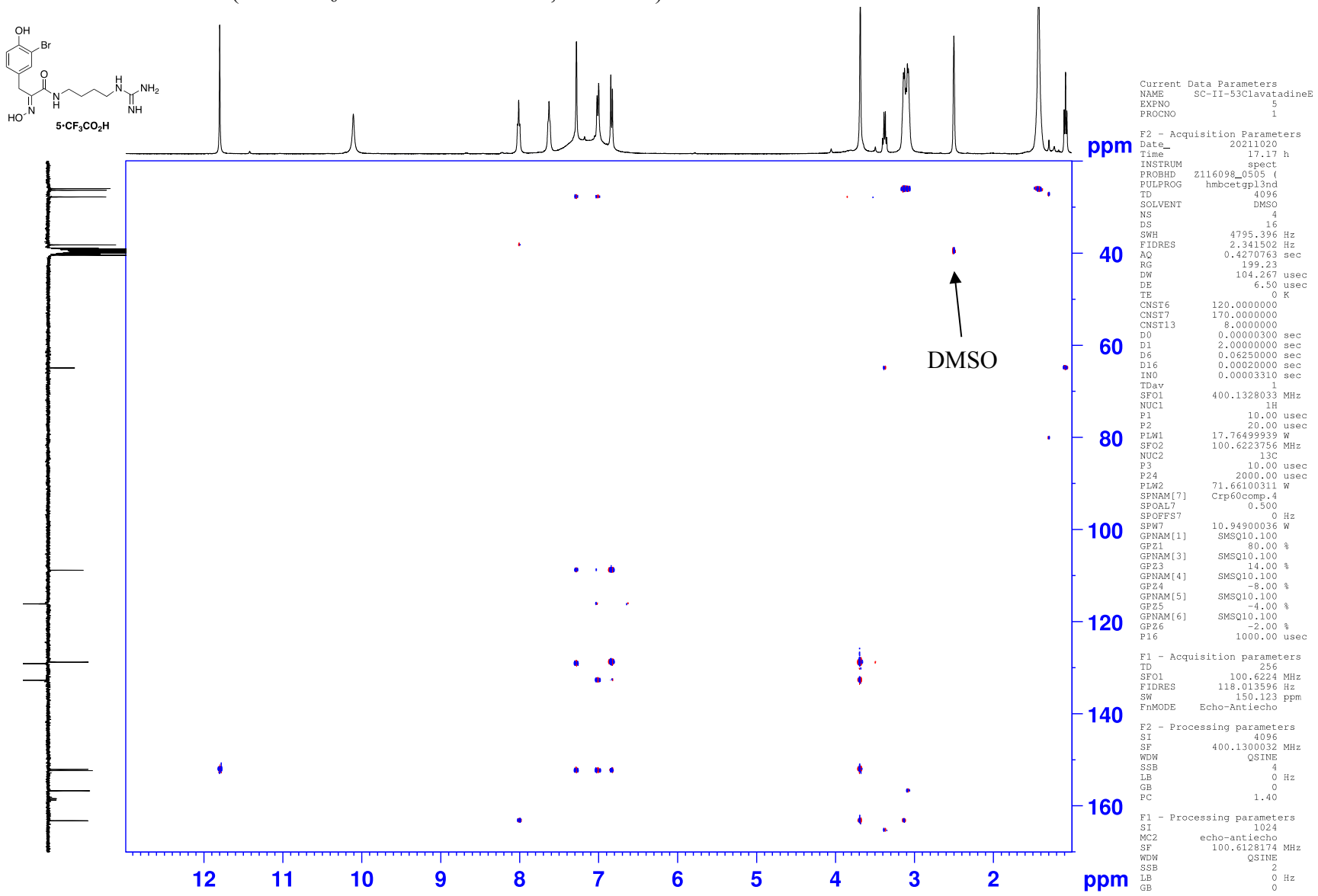


Figure S15. ^{1}H-^{13}C HMBC NMR (400 MHz, DMSO-d_6) spectrum of unpurified, synthetic clavatadine E (**5**).

^{13}C DEPTQ-135 NMR (CD_3OD with 0.03% v/v TMS, 100 MHz)

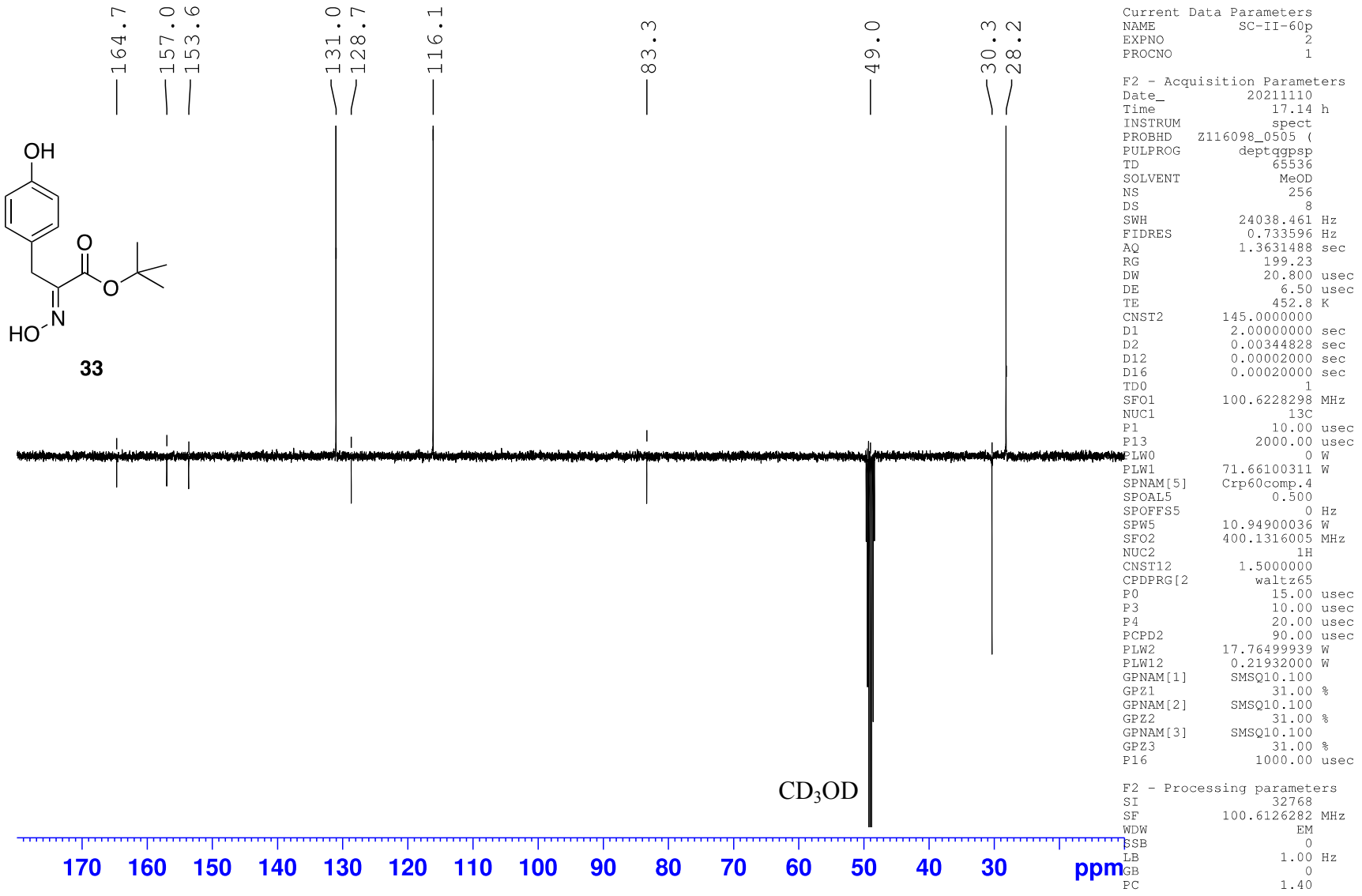


Figure S16. ^{13}C DEPTQ-135 NMR (100 MHz, CD_3OD) spectrum of the known compound **33**.

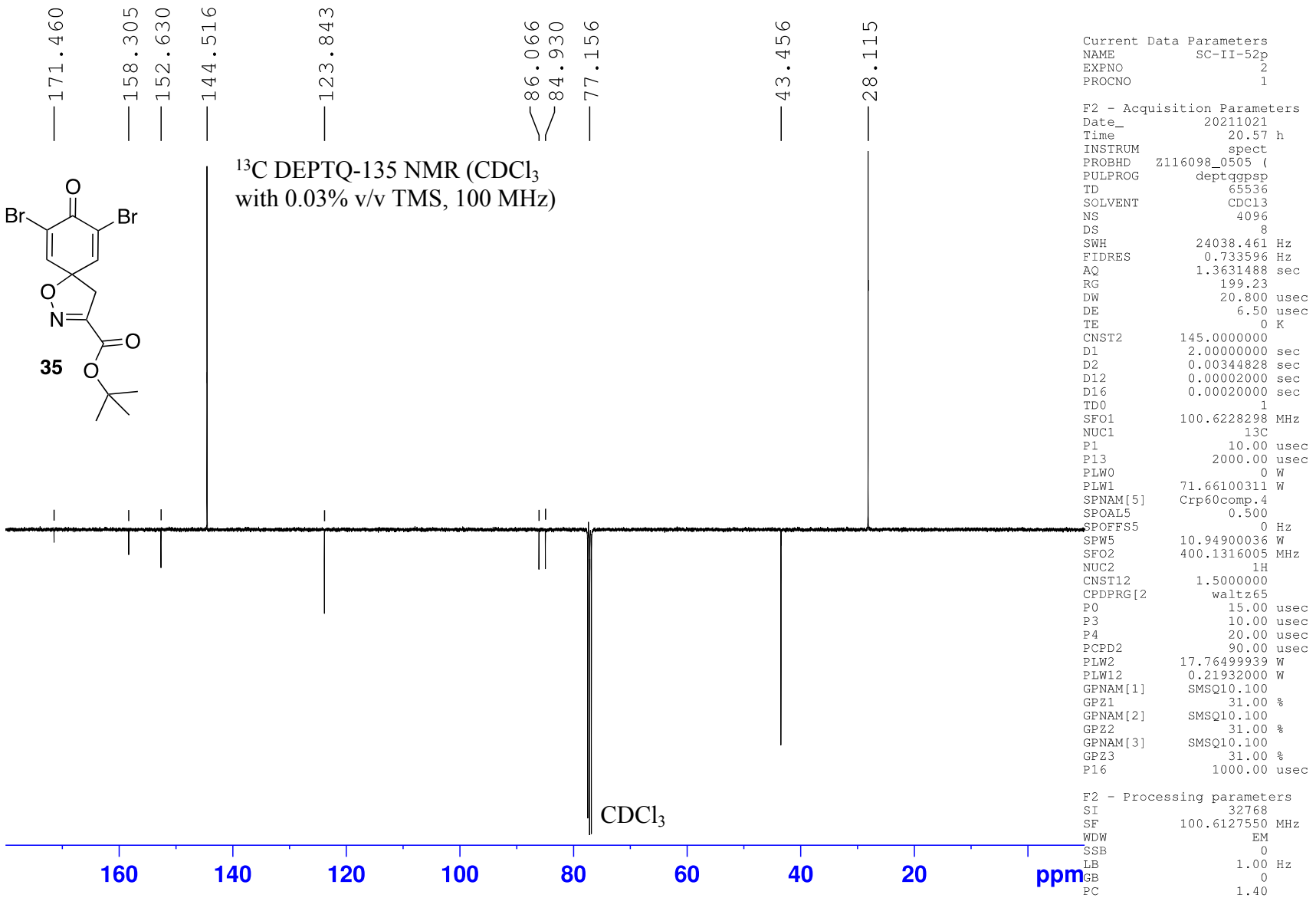


Figure S17. ^{13}C DEPTQ-135 NMR (100 MHz, $CDCl_3$) spectrum of the known compound **35**.

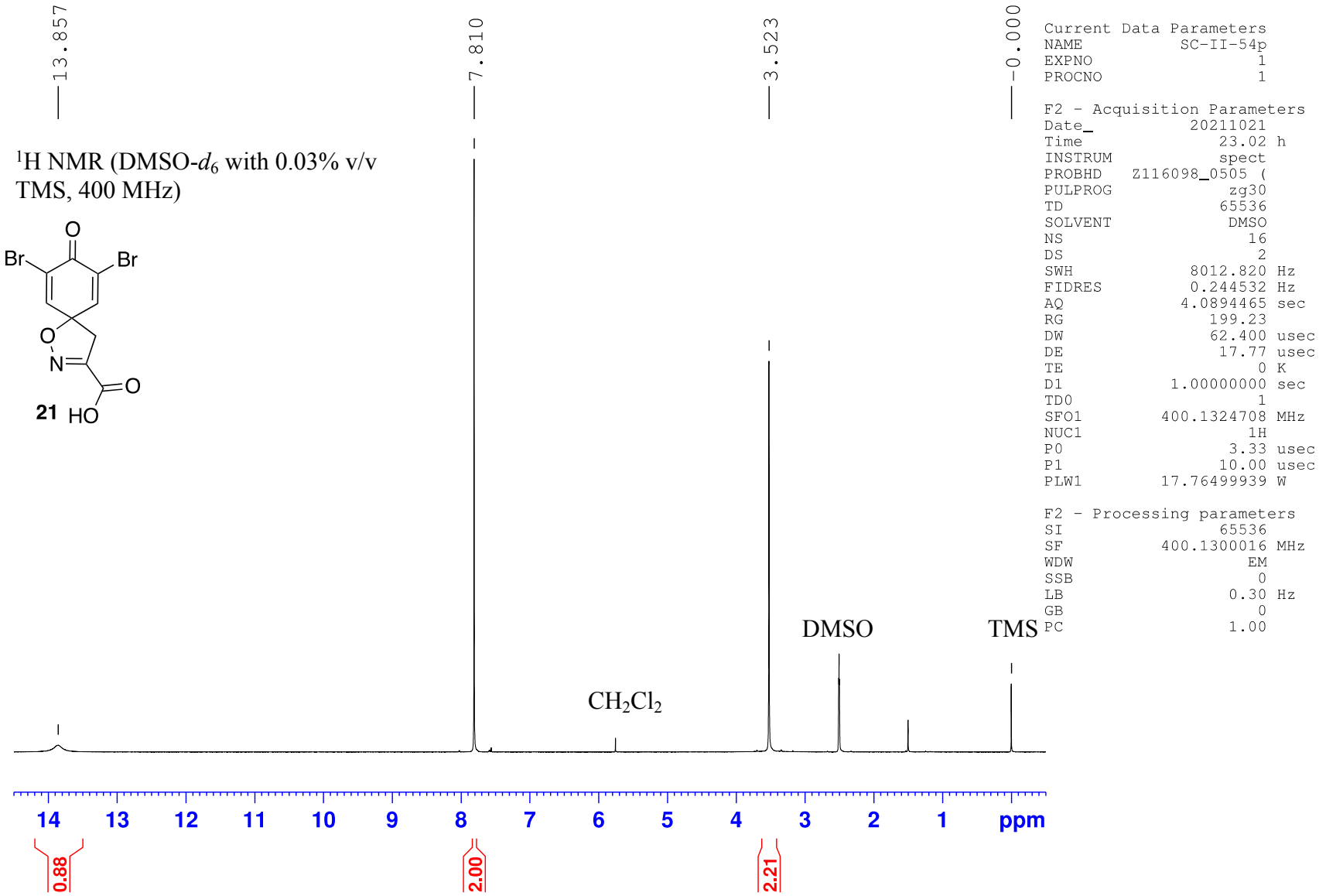


Figure S18. ^{1}H NMR (400 MHz, DMSO-d_6) spectrum of the known compound **21**.

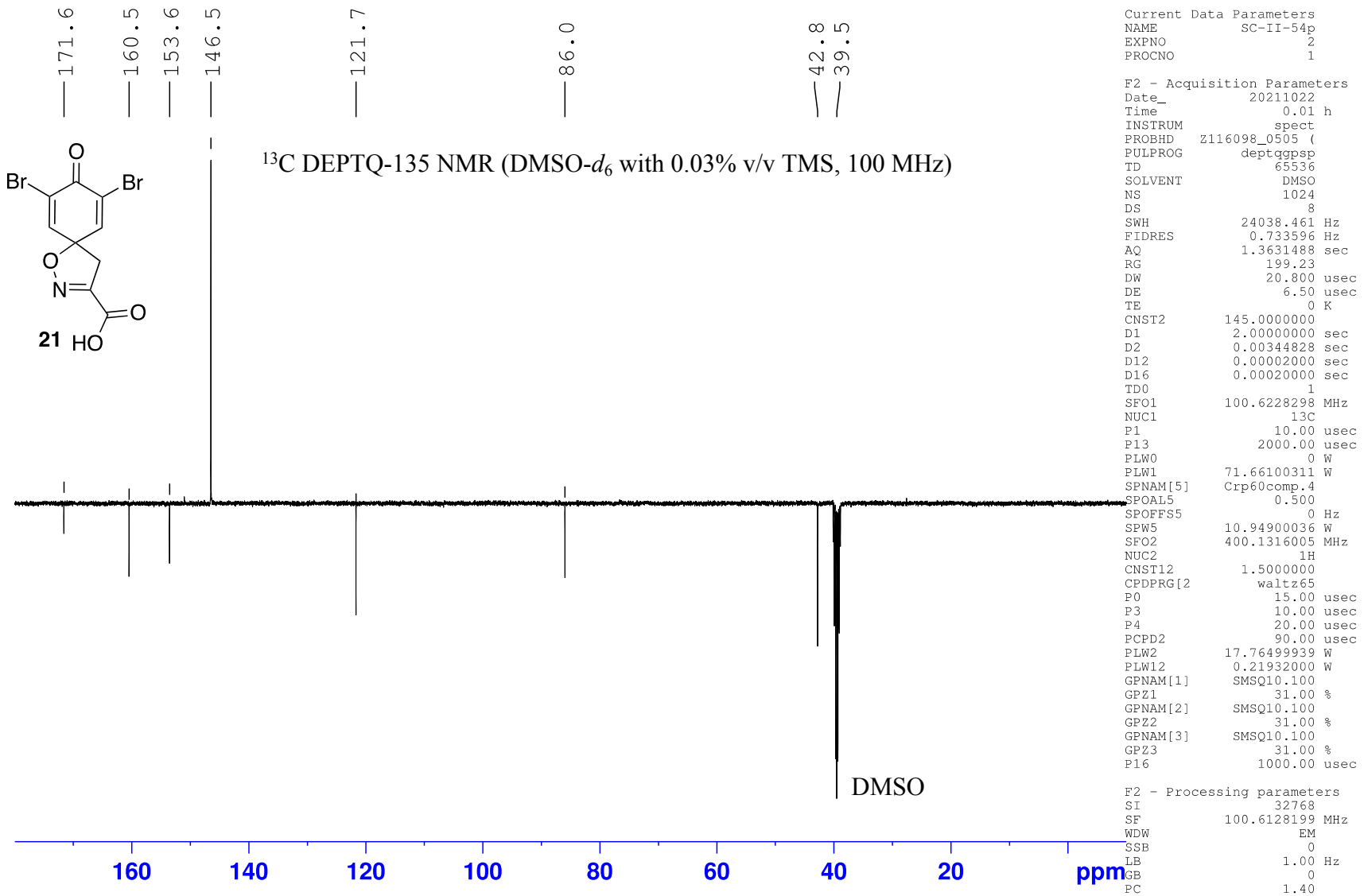


Figure S19. ^{13}C DEPTQ-135 NMR (100 MHz, DMSO-d_6) spectrum of the known compound **21**.

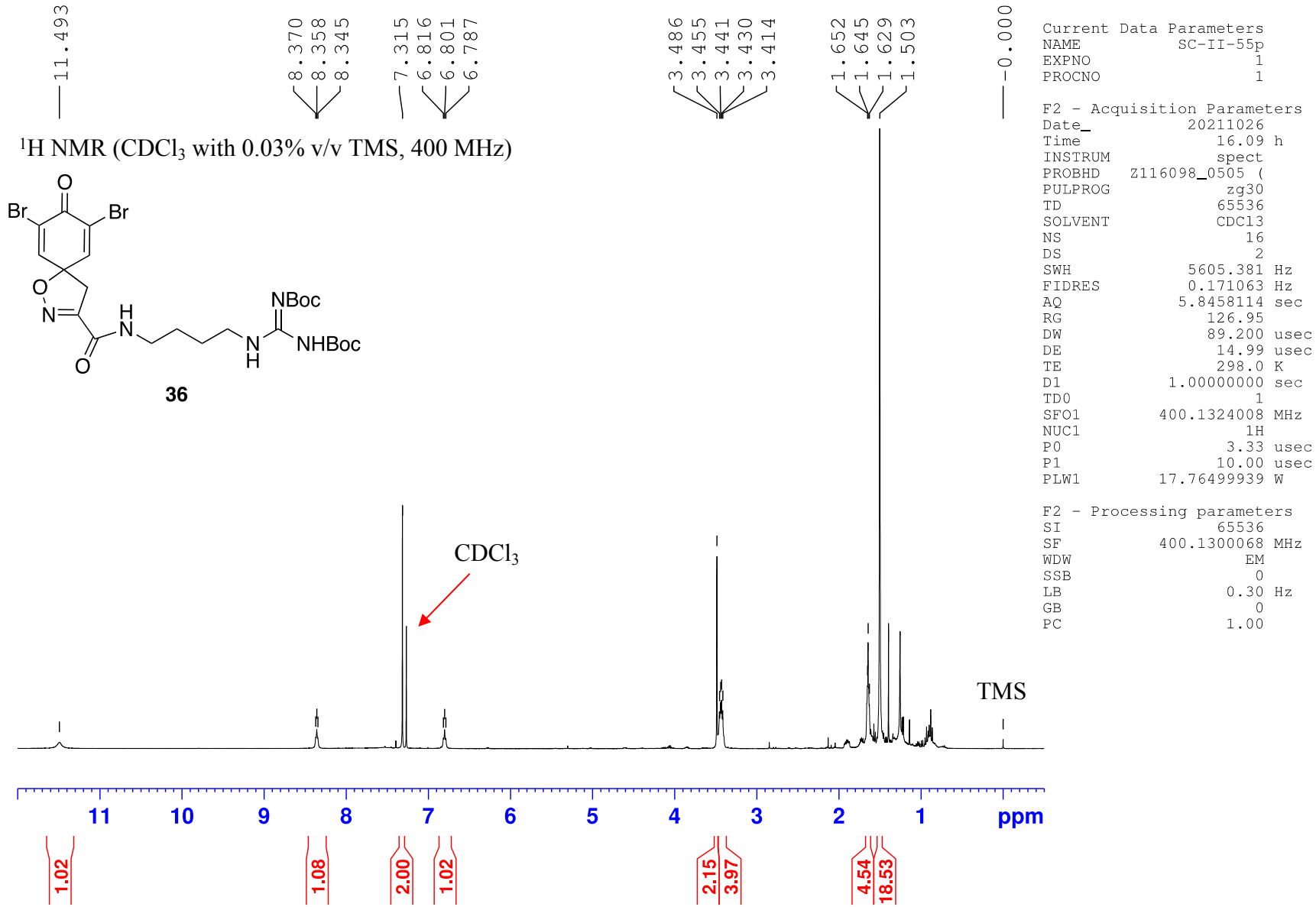


Figure S20. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the known compound **36**.

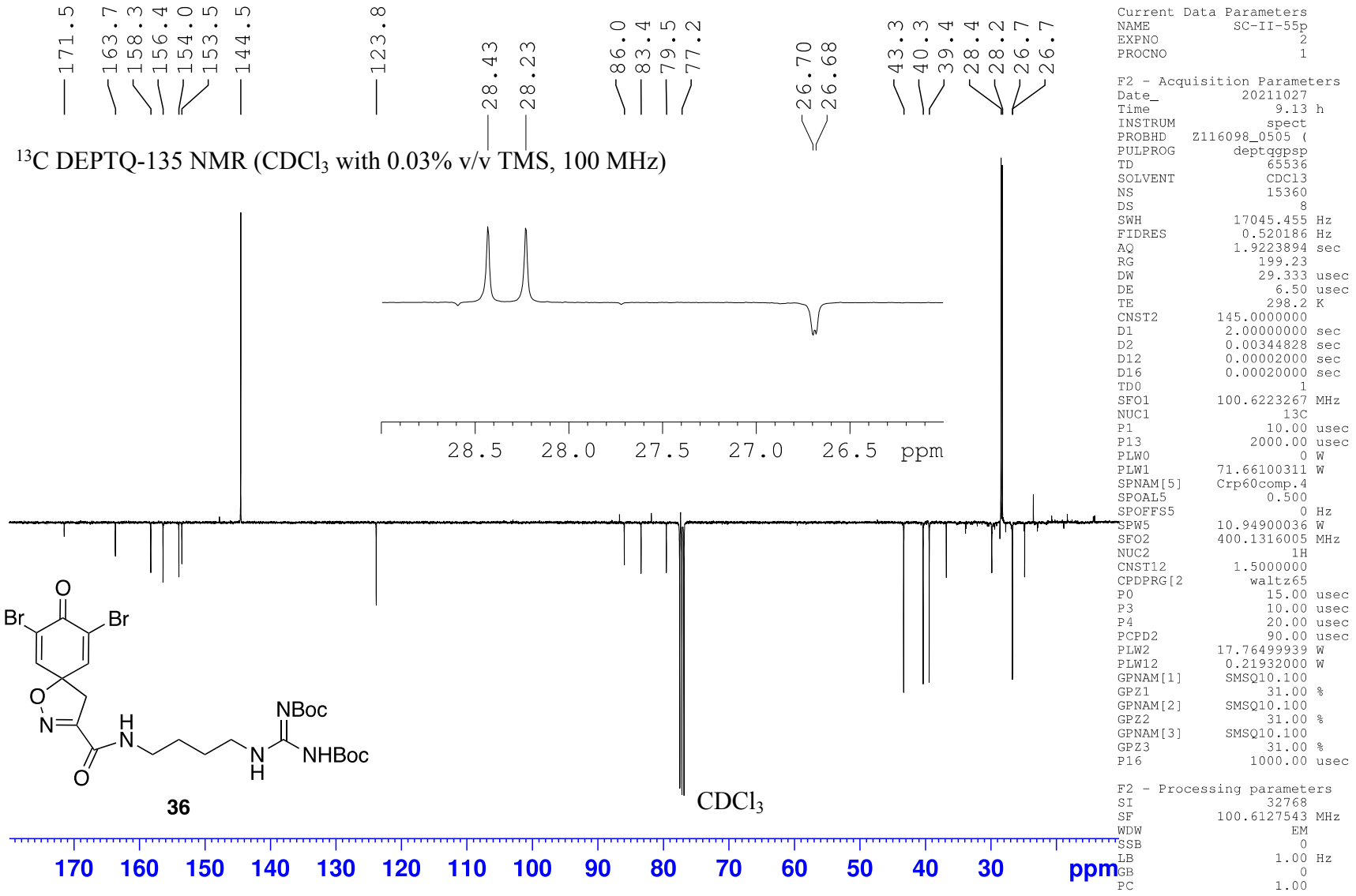
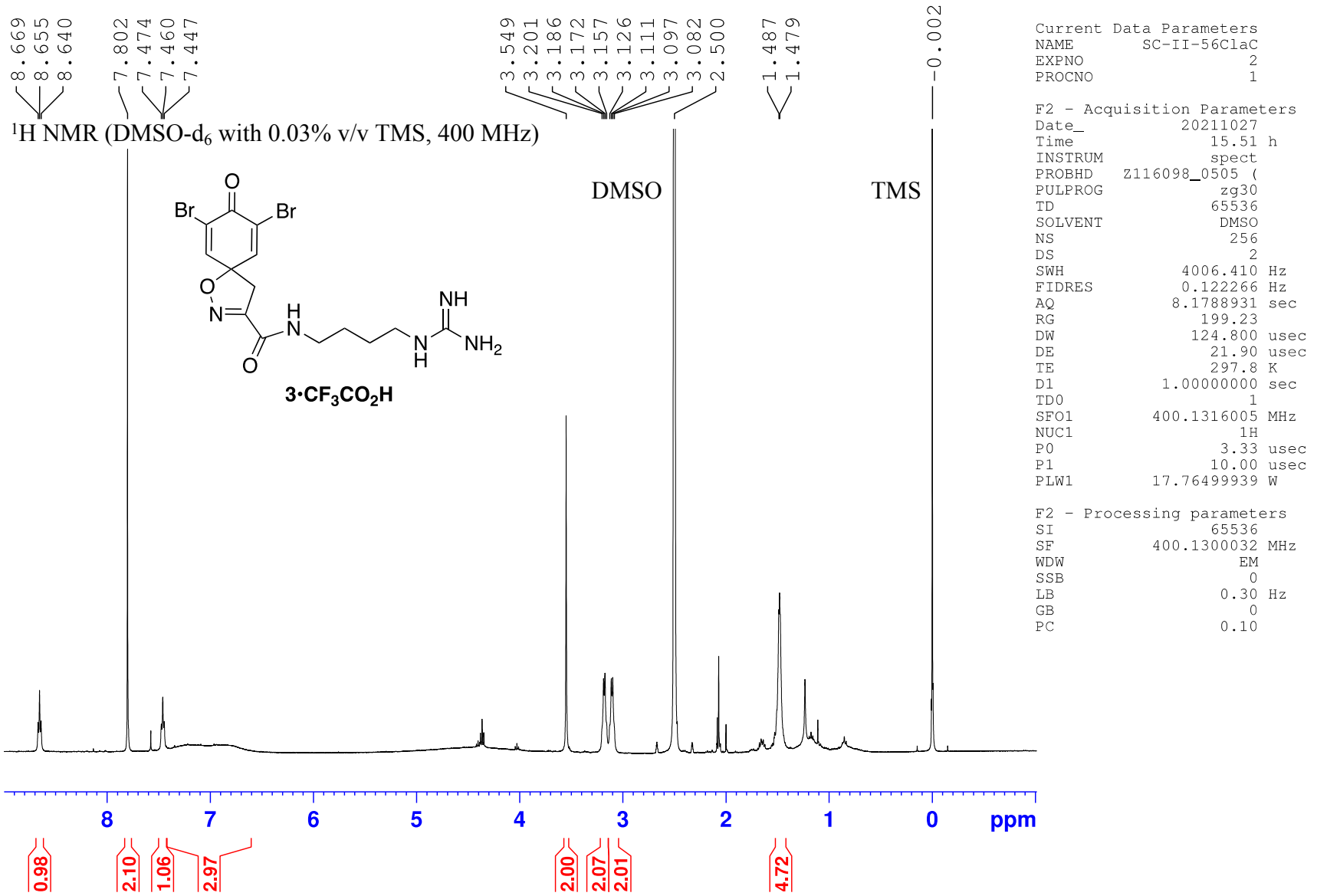


Figure S21. ^{13}C DEPTQ-135 NMR (100 MHz, $CDCl_3$) spectrum of the known compound **36**.

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Current Data Parameters
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EXPNO                  2
PROCNO                 1

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Time               15.51 h
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PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                   256
DS                     2
SWH             4006.410 Hz
FIDRES          0.122266 Hz
AQ              8.1788931 sec
RG                 199.23
DW                124.800 usec
DE                 21.90 usec
TE                 297.8 K
D1            1.00000000 sec
TD0                    1
SFO1         400.1316005 MHz
NUC1                  1H
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P1                10.00 usec
PLW1         17.76499939 W

F2 - Processing parameters
SI                 65536
SF           400.1300032 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  0.10
```
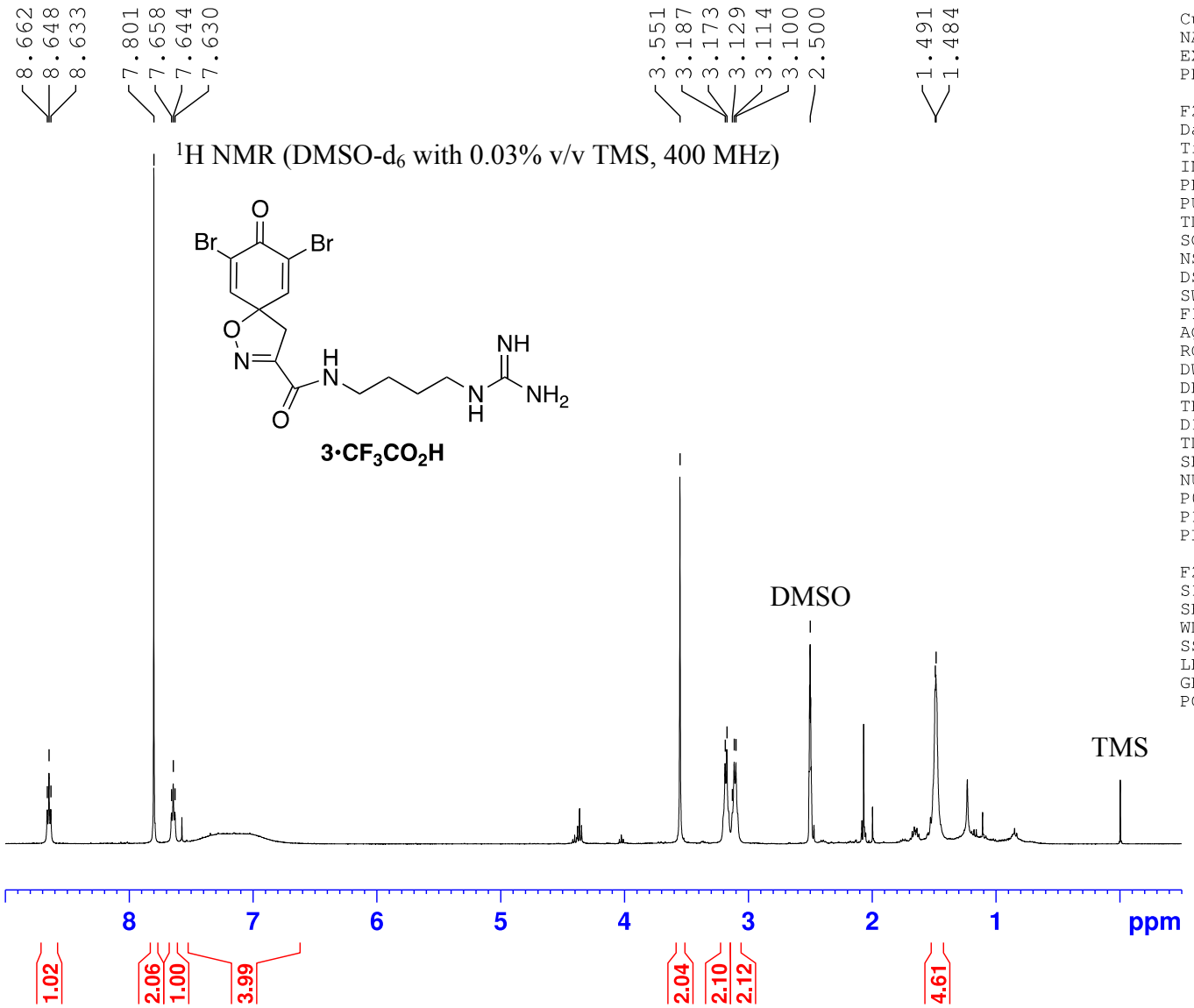

Figure S22. ^{1}H NMR (400 MHz, DMSO-d$_6$) spectrum of dilute, unpurified, synthetic clavatadine C (**3**).

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Current Data Parameters
NAME        SC-II-56ClaC
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PROCNO                 1

F2 - Acquisition Parameters
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Time               10.25 h
INSTRUM             spect
PROBHD   Z116098_0505 (
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                    16
DS                     2
SWH             5201.109 Hz
FIDRES          0.158725 Hz
AQ              6.3001943 sec
RG                 142.71
DW                 96.133 usec
DE                 16.61 usec
TE                 298.7 K
D1              1.00000000 sec
TD0                    1
SFO1          400.1322007 MHz
NUC1                  1H
P0                  3.33 usec
P1                 10.00 usec
PLW1          17.76499939 W

F2 - Processing parameters
SI                 65536
SF            400.1300032 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  0.01
```

Figure S23. ^{1}H NMR (400 MHz, DMSO-d$_6$) spectrum of concentrated, unpurified, synthetic clavatadine C (**3**).

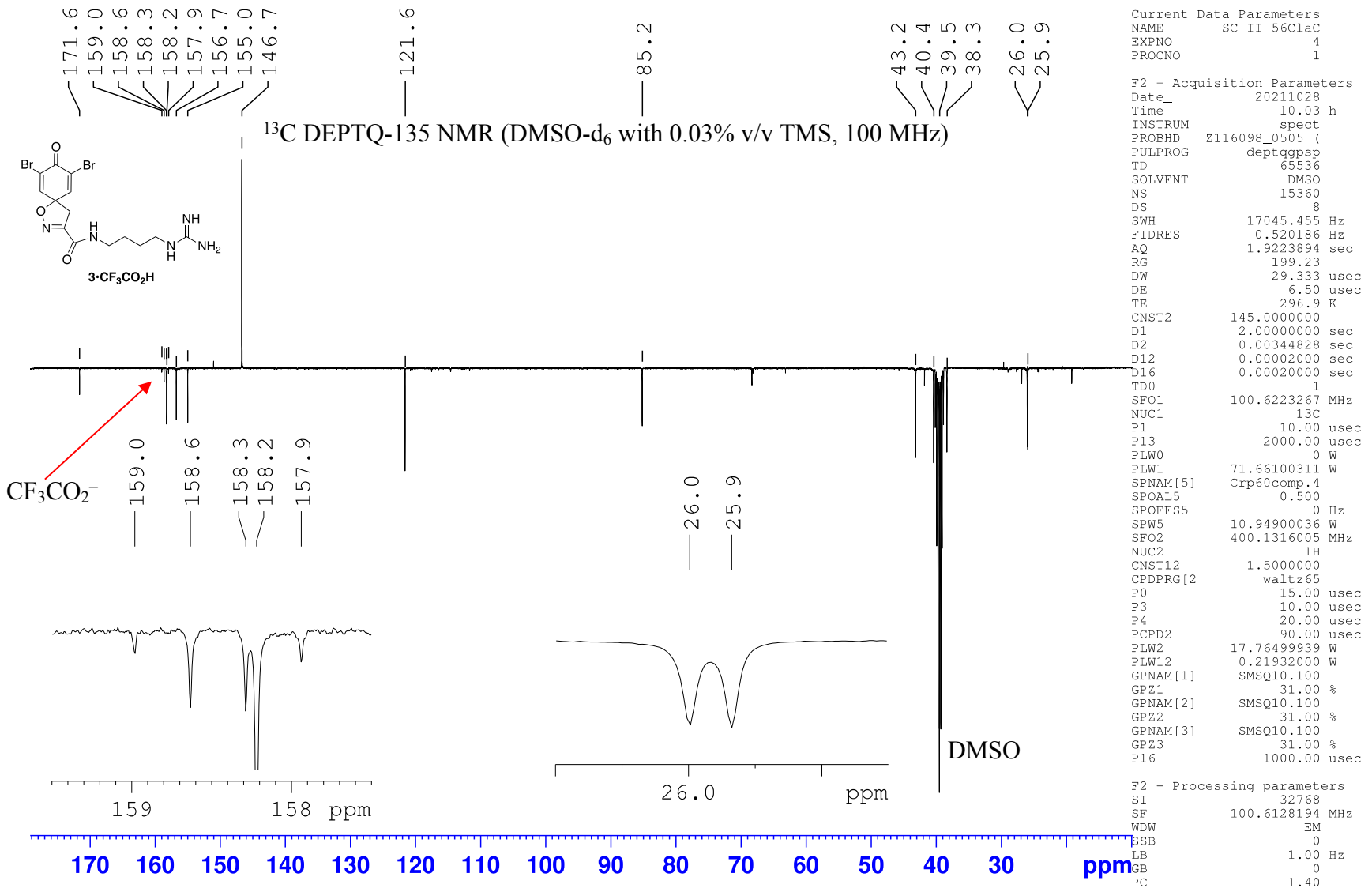


Figure S24. ^{13}C DEPTQ-135 NMR (100 MHz, DMSO-d_6) spectrum of unpurified, synthetic clavatadine C (**3**).

^{1}H-^{1}H COSY NMR (DMSO-d_6 with 0.03% v/v TMS, 400 MHz)

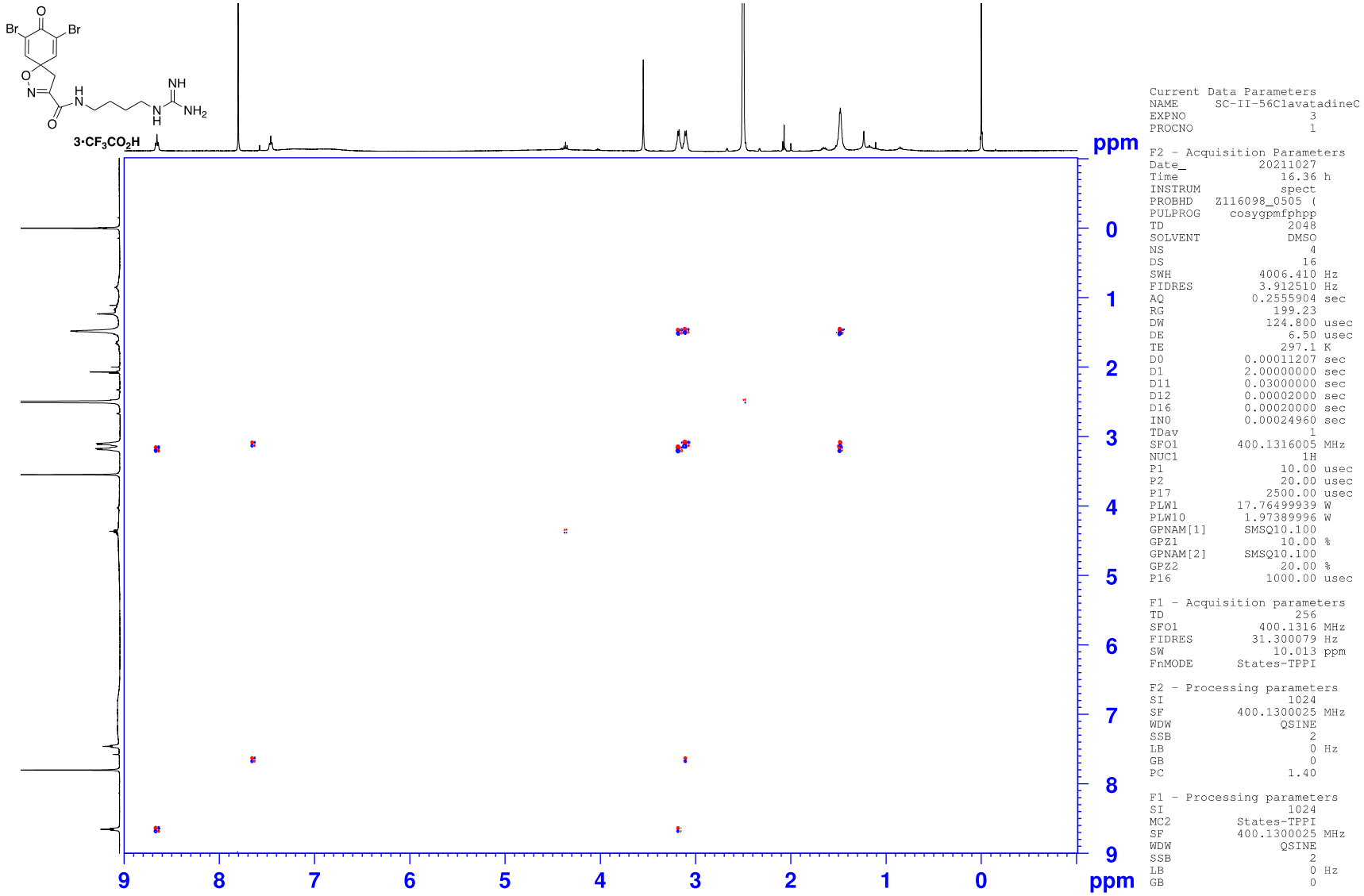


Figure S25. ^{1}H-^{1}H COSY NMR (400 MHz, DMSO-d_6) spectrum of unpurified, synthetic clavatadine C (**3**).

^{1}H-^{13}C Multiplicity-edited HSQC NMR (DMSO-d_6 with 0.03% v/v TMS, 400 MHz)

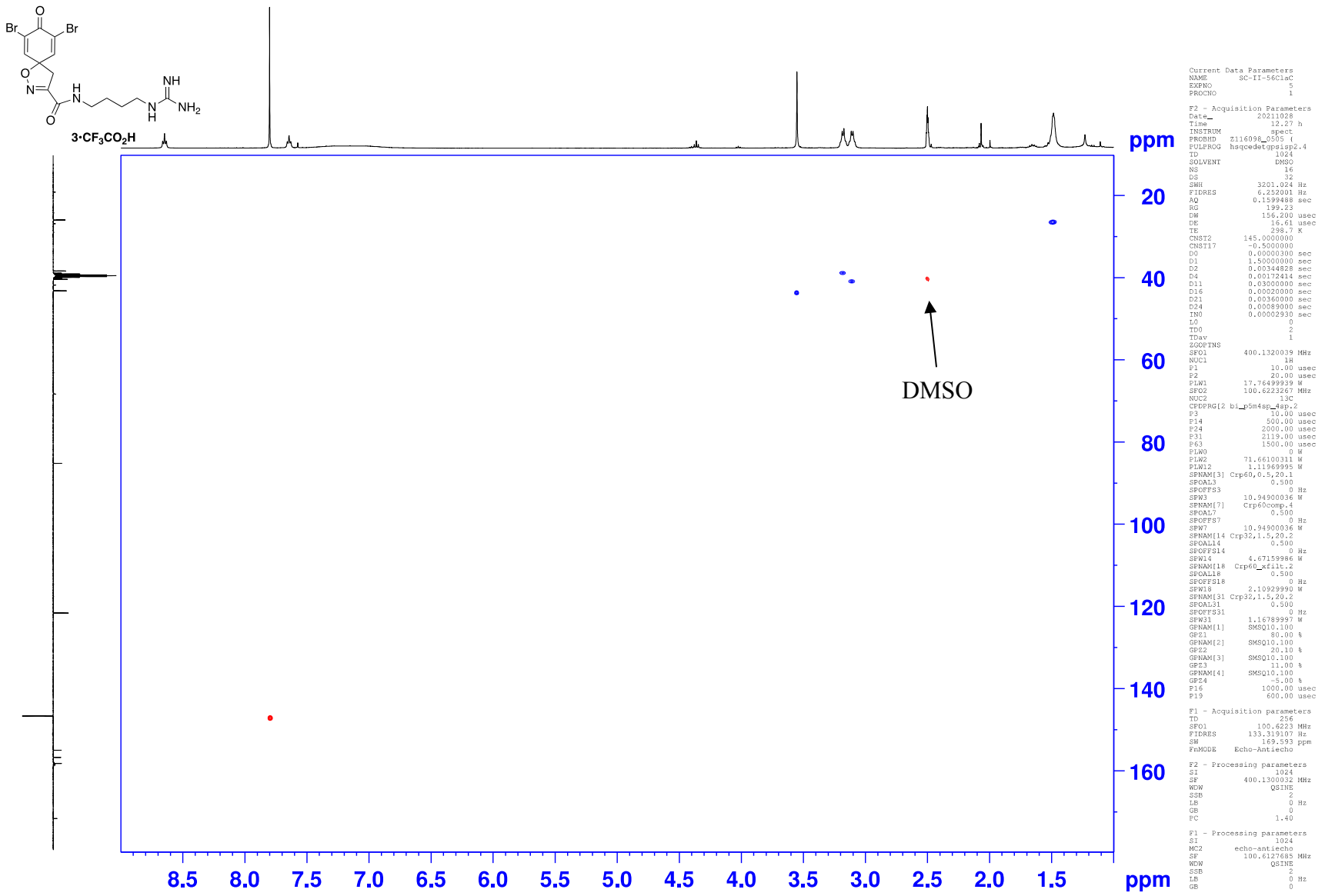


Figure S26. ^{1}H-^{13}C Multiplicity Edited HSQC NMR (400 MHz, DMSO-d_6) spectrum of unpurified, synthetic clavatadine C (**3**).

^{1}H-^{13}C HMBC NMR (DMSO-d_6 with 0.03% v/v TMS, 400 MHz)

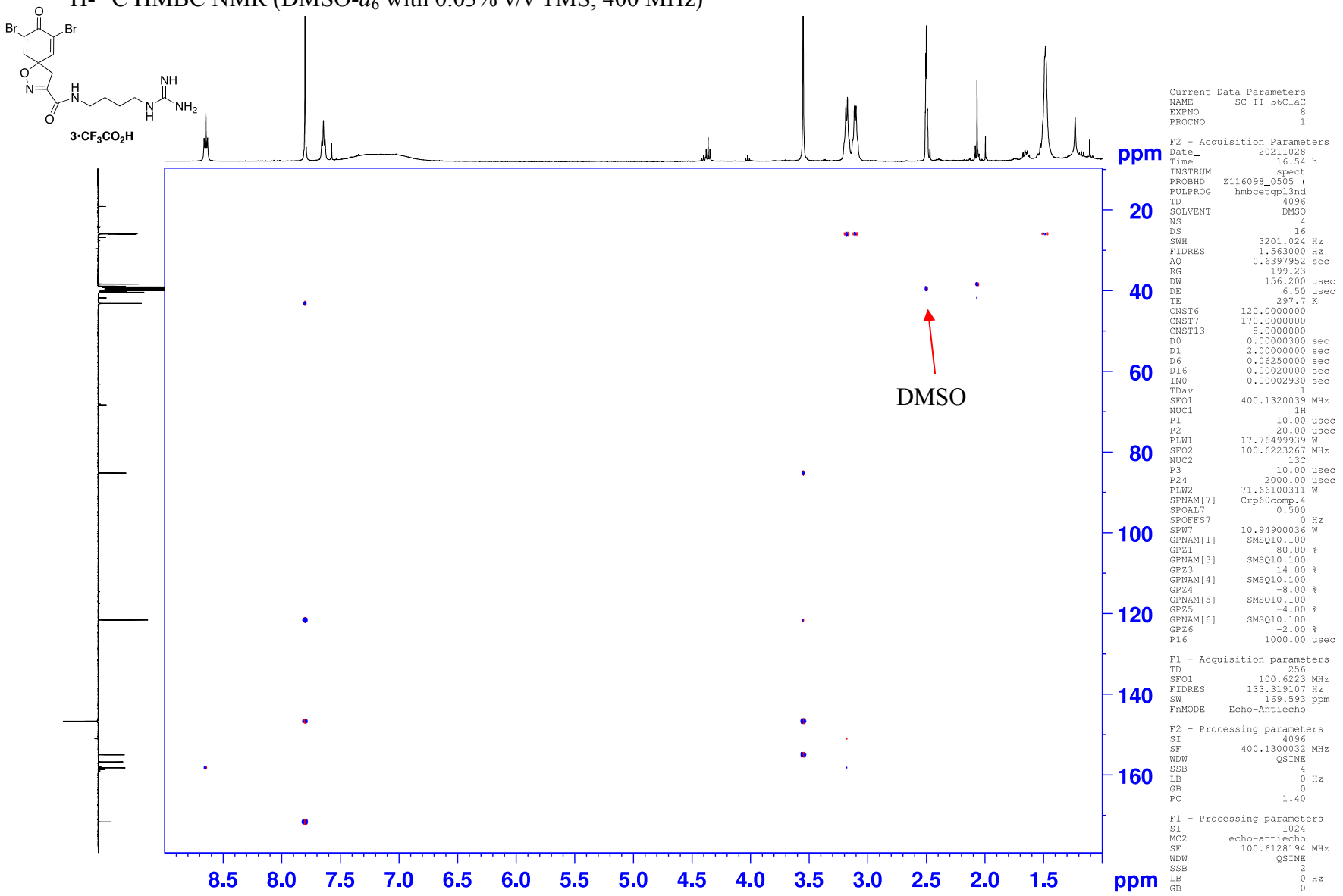
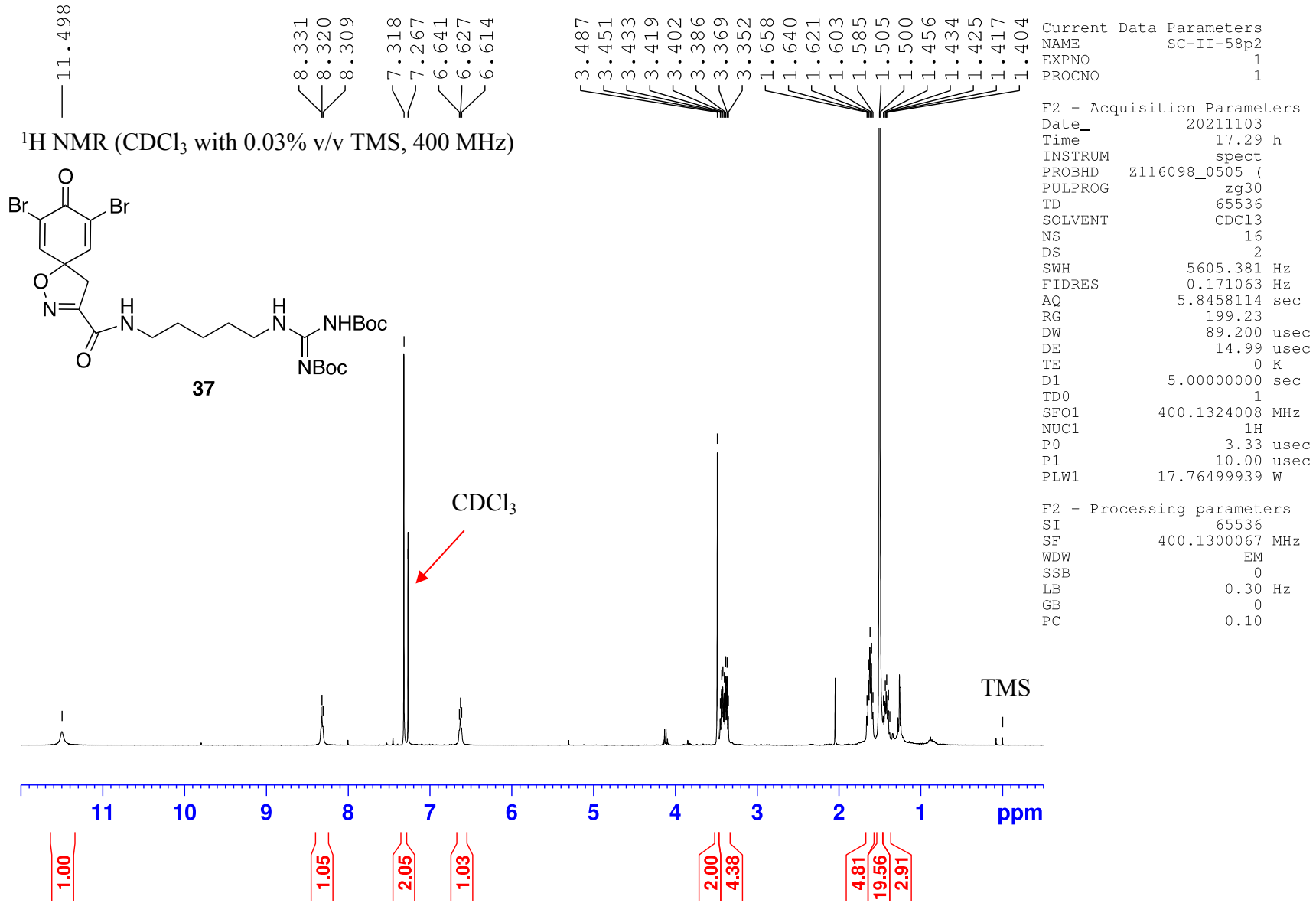


Figure S27. ^{1}H-^{13}C HMBC NMR (400 MHz, DMSO-d_6) spectrum of unpurified, synthetic clavatadine C (**3**).



^{1}H NMR ($CDCl_3$ with 0.03% v/v TMS, 400 MHz)

Figure S28. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the new compound **37**.

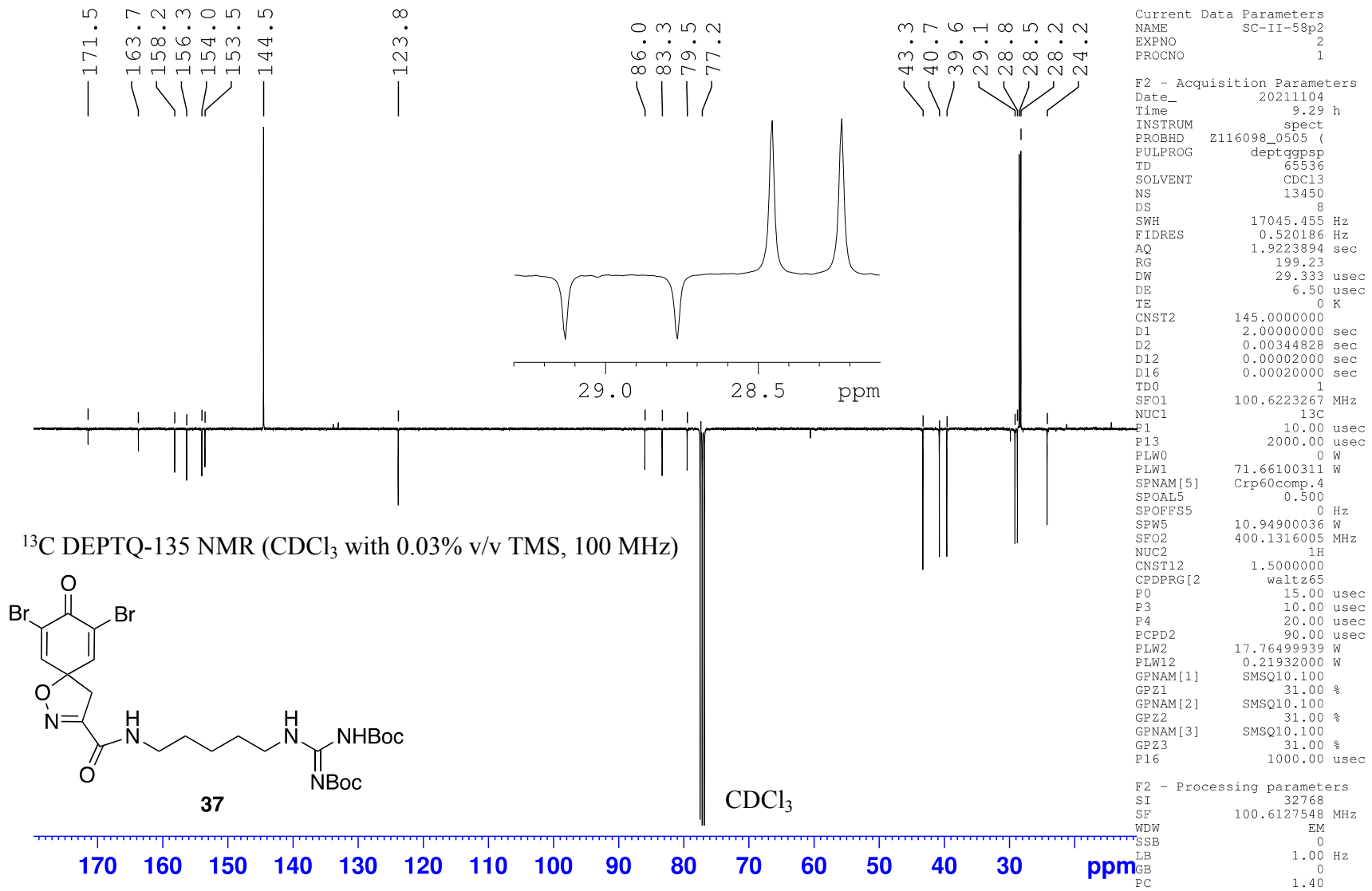


Figure S29. ^{13}C DEPTQ-135 NMR (100 MHz, $CDCl_3$) spectrum of the new compound **37**.

^{1}H-^{1}H COSY NMR ($CDCl_3$ with 0.03% v/v TMS, 400 MHz)

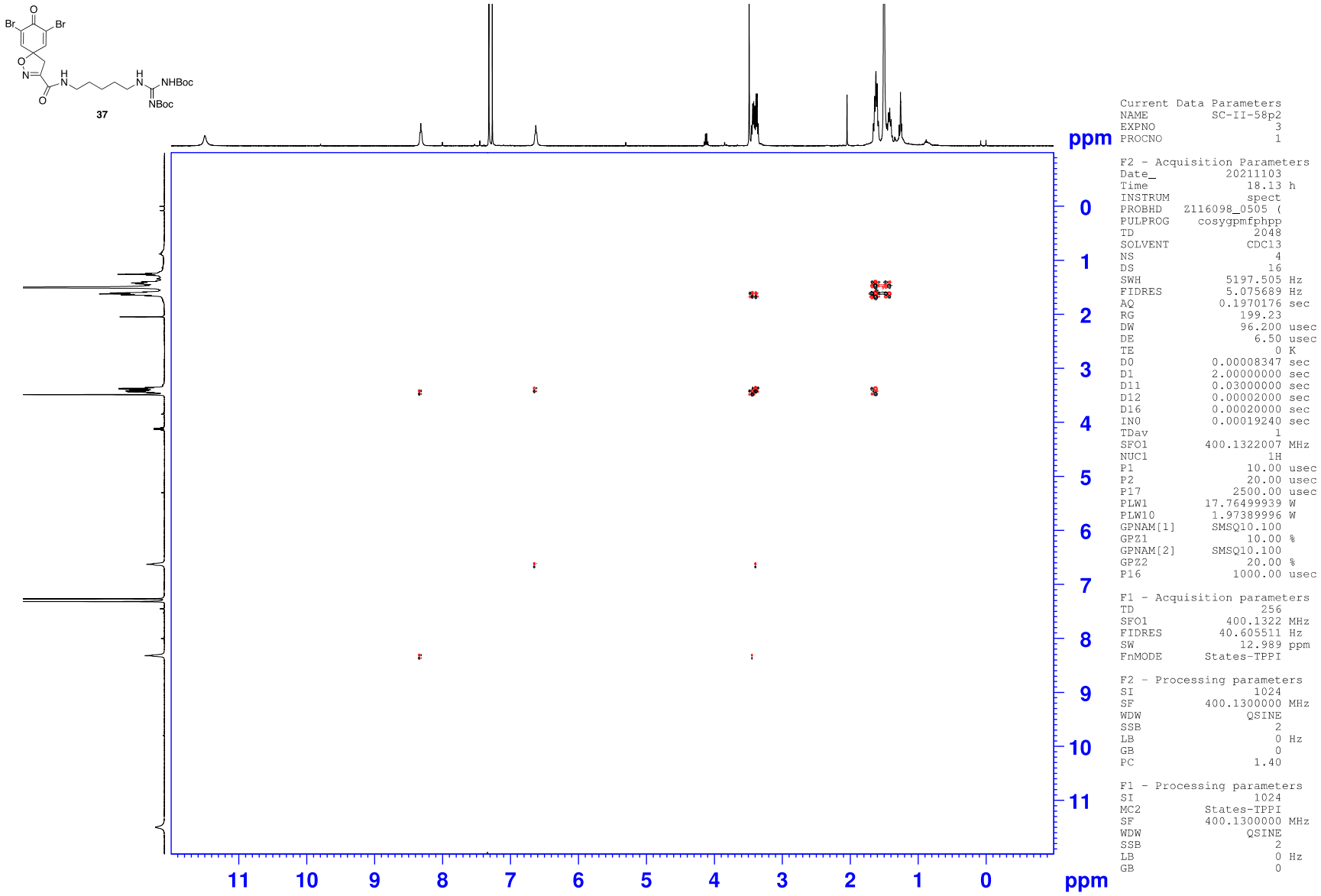
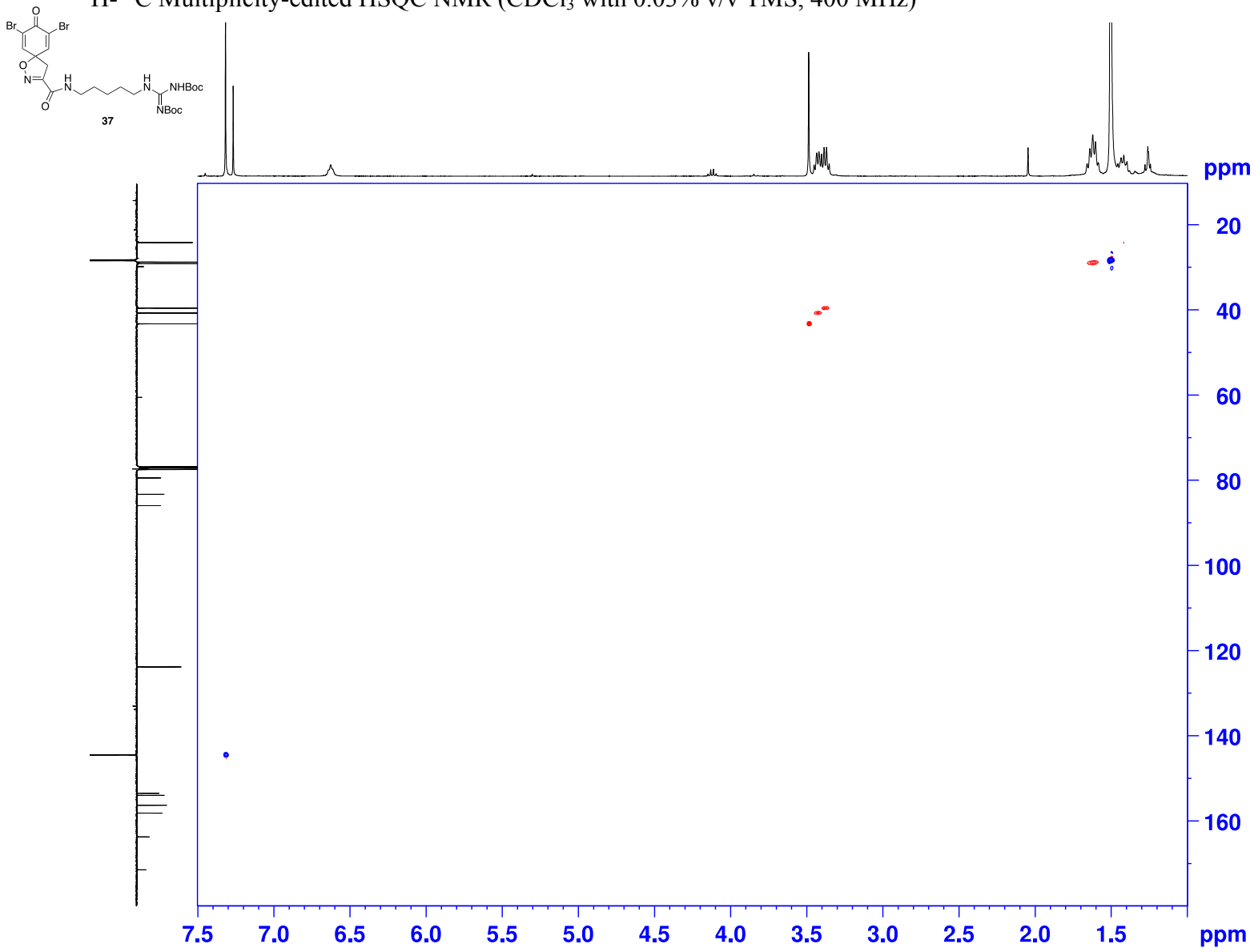


Figure S30. ^{1}H-^{1}H COSY NMR (400 MHz, $CDCl_3$) spectrum of the new compound **37**.

^{1}H-^{13}C Multiplicity-edited HSQC NMR ($CDCl_3$ with 0.03% v/v TMS, 400 MHz)



Current Data Parameters
NAME SC-II-58p2
EXPNO 4
PROCNO 1

F2 - Acquisition Parameters
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Time 10.36 h
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PROBHD Z116098_0505 (
PULPROG hsqcedetgpsisp2.4
TD 1024
SOLVENT CDCl3
NS 8
DS 32
SWH 2602.359 Hz
FIDRES 5.082733 Hz
AQ 0.1967445 sec
RG 199.23
DW 192.133 usec
DE 18.97 usec
TE 0 K
CNST2 145.0000000
CNST17 -0.5000000
D0 0.00000300 sec
D1 1.50000000 sec
D2 0.00344828 sec
D4 0.00172414 sec
D11 0.03000000 sec
D16 0.00200000 sec
D21 0.00360000 sec
D24 0.00089000 sec
IN0 0.00002930 sec
L0 0
TD0 2
TDav 1
ZGOPTNS
SFO1 400.1317074 MHz
NUC1 1H
P1 10.00 usec
P2 20.00 usec
PLW1 17.76499939 W
SFO2 100.6223267 MHz
NUC2 13C
CPDPRG[2 bi_p5m4sp_4sp.2
P3 10.00 usec
P14 500.00 usec
P24 2000.00 usec
P31 2119.00 usec
P63 1500.00 usec
PLW0 0 W
PLW2 71.66100311 W
PLW12 1.11969995 W
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SPOFFS3 0 Hz
SPW3 10.94900036 W
SPNAM[7] Crp60comp.4
SPOAL7 0.500
SPOFFS7 0 Hz
SPW7 10.94900036 W
SPNAM[14 Crp32,1.5,20.2
SPOAL14 0.500
SPOFFS14 0 Hz
SPW14 4.67159986 W
SPNAM[18 Crp60_xfilt.2
SPOAL18 0.500
SPOFFS18 0 Hz
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SPOAL31 0.500
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GPZ3 11.00 %
GPNAM[4] SMSQ10.100
GPZ4 -5.00 %
P16 1000.00 usec
P19 600.00 usec

F1 - Acquisition parameters
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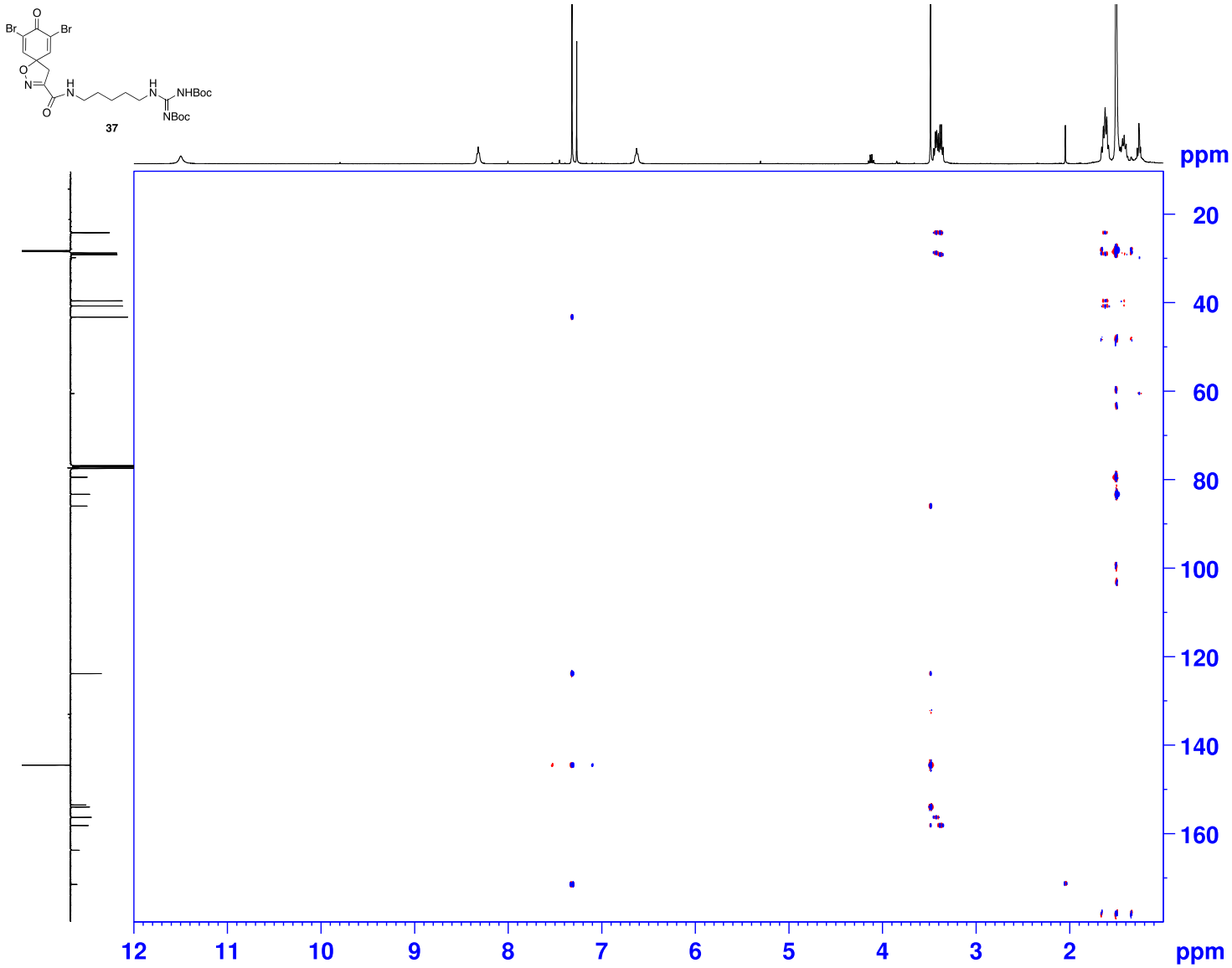
SFO1 100.6223 MHz
FIDRES 133.319107 Hz
SW 169.593 ppm
FnMODE Echo-Antiecho

F2 - Processing parameters
SI 1024
SF 400.1300067 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0
PC 1.40

F1 - Processing parameters
SI 1024
MC2 echo-antiecho
SF 100.6127548 MHz
WDW QSINE
SSB 2
LB 0 Hz
GB 0

Figure S31. ^{1}H-^{13}C Multiplicity Edited HSQC NMR (400 MHz, $CDCl_3$) spectrum of the new compound **37**.

^{1}H-^{13}C HMBC NMR ($CDCl_3$ with 0.03% v/v TMS, 400 MHz)

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Current Data Parameters
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EXPNO                          5
PROCNO                         1

F2 - Acquisition Parameters
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Time                       12.17 h
INSTRUM                    spect
PROBHD    Z116098_0505 (
PULPROG     hmbcetgpl3nd
TD                          4096
SOLVENT                   CDCl3
NS                             8
DS                            16
SWH                     4401.409 Hz
FIDRES                  2.149125 Hz
AQ                      0.4653056 sec
RG                         199.23
DW                        113.600 usec
DE                          6.50 usec
TE                             0 K
CNST6                120.0000000
CNST7                170.0000000
CNST13                 8.0000000
D0                     0.00000300 sec
D1                     2.00000000 sec
D6                     0.06250000 sec
D16                    0.00020000 sec
IN0                    0.00002930 sec
TDav                           1
SFO1                400.1326076 MHz
NUC1                        1H
P1                         10.00 usec
P2                         20.00 usec
PLW1                17.76499939 W
SFO2                100.6223267 MHz
NUC2                        13C
P3                         10.00 usec
P24                      2000.00 usec
PLW2                71.66100311 W
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SPOFFS7                        0 Hz
SPW7                10.94900036 W
GPNAM[1]             SMSQ10.100
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GPNAM[3]             SMSQ10.100
GPZ3                       14.00 %
GPNAM[4]             SMSQ10.100
GPZ4                       -8.00 %
GPNAM[5]             SMSQ10.100
GPZ5                       -4.00 %
GPNAM[6]             SMSQ10.100
GPZ6                       -2.00 %
P16                      1000.00 usec

F1 - Acquisition parameters
TD                           256
SFO1                  100.6223 MHz
FIDRES                133.319107 Hz
SW                       169.593 ppm
FnMODE            Echo-Antiecho

F2 - Processing parameters
SI                          4096
SF                    400.1300067 MHz
WDW                        QSINE
SSB                            4
LB                             0 Hz
GB                             0
PC                          1.40

F1 - Processing parameters
SI                          1024
MC2                 echo-antiecho
SF                    100.6127548 MHz
WDW                        QSINE
SSB                            2
LB                             0 Hz
GB                             0
```
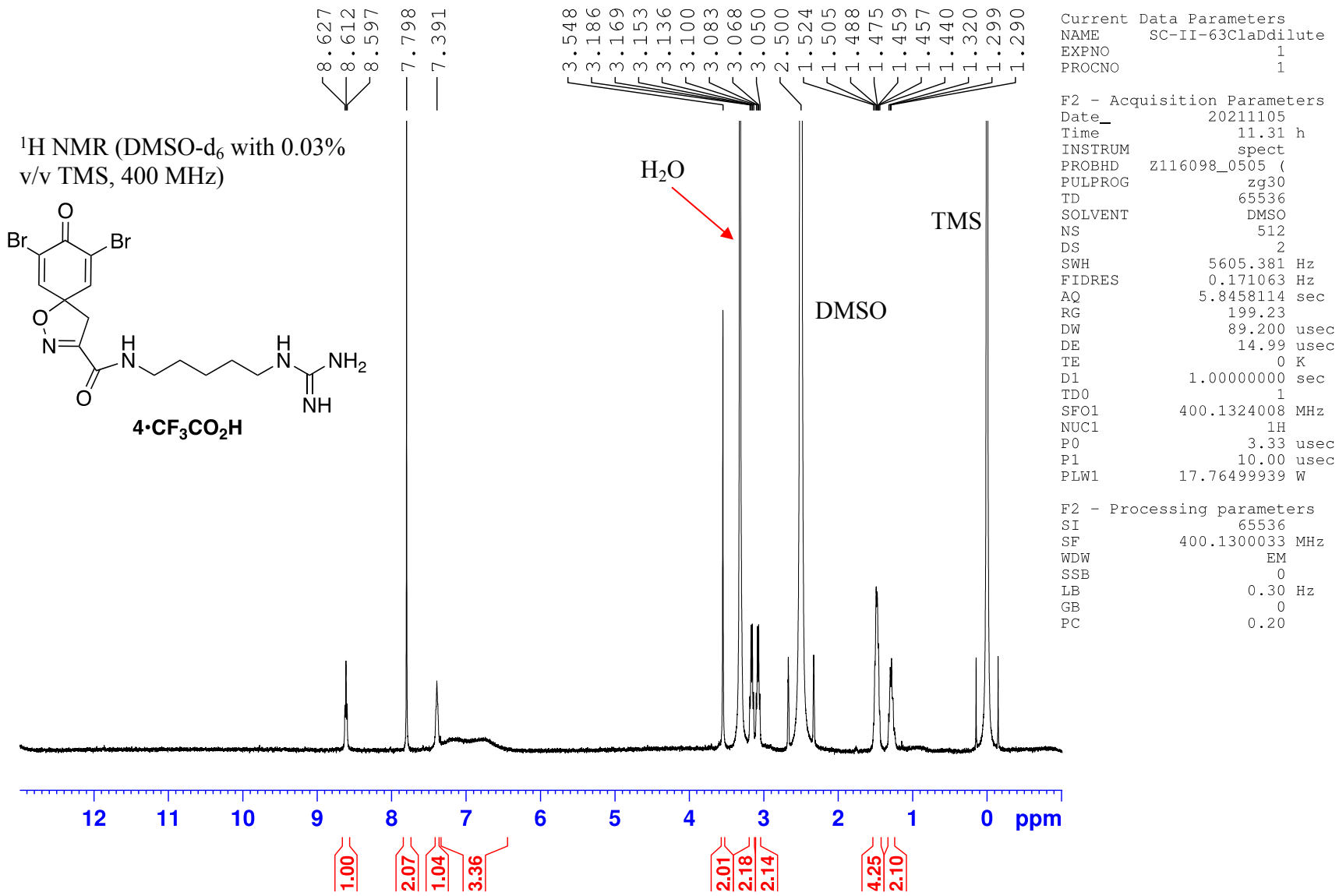

Figure S32. ^{1}H-^{13}C HMBC NMR (400 MHz, $CDCl_3$) spectrum of the new compound **37**.

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Current Data Parameters
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PROCNO                   1

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PROBHD   Z116098_0505 (
PULPROG             zg30
TD                 65536
SOLVENT             DMSO
NS                   512
DS                     2
SWH            5605.381 Hz
FIDRES         0.171063 Hz
AQ             5.8458114 sec
RG                199.23
DW                89.200 usec
DE                14.99 usec
TE                    0 K
D1            1.00000000 sec
TD0                    1
SFO1         400.1324008 MHz
NUC1                  1H
P0                 3.33 usec
P1                10.00 usec
PLW1         17.76499939 W

F2 - Processing parameters
SI                 65536
SF           400.1300033 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 0.20
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Figure S33. ^{1}H NMR (400 MHz, DMSO-d$_6$) spectrum of dilute, unpurified, synthetic clavatadine D (**4**).

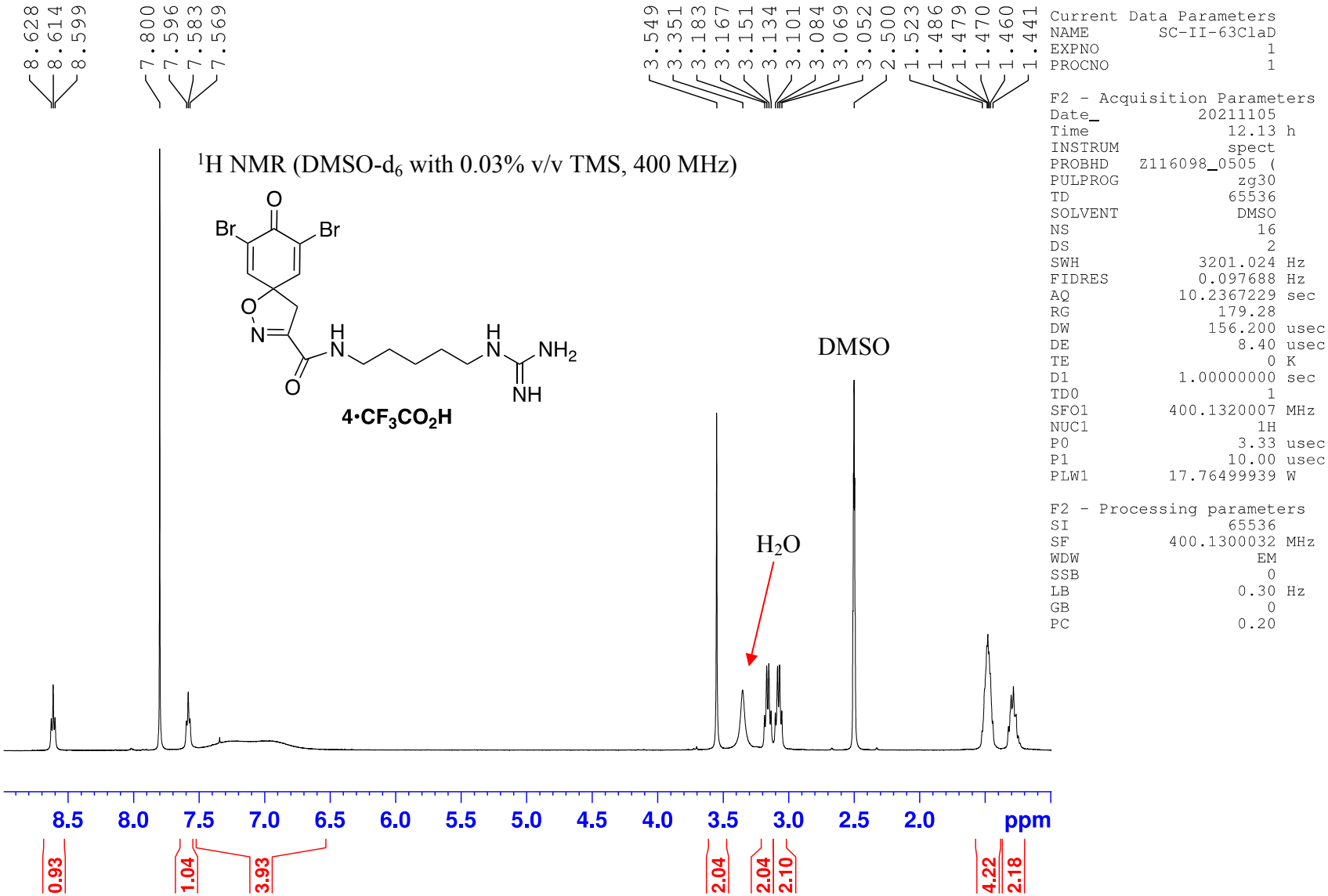

Figure S34. ^{1}H NMR (400 MHz, DMSO-d$_6$) spectrum of concentrated, unpurified, synthetic clavatadine D (**4**).

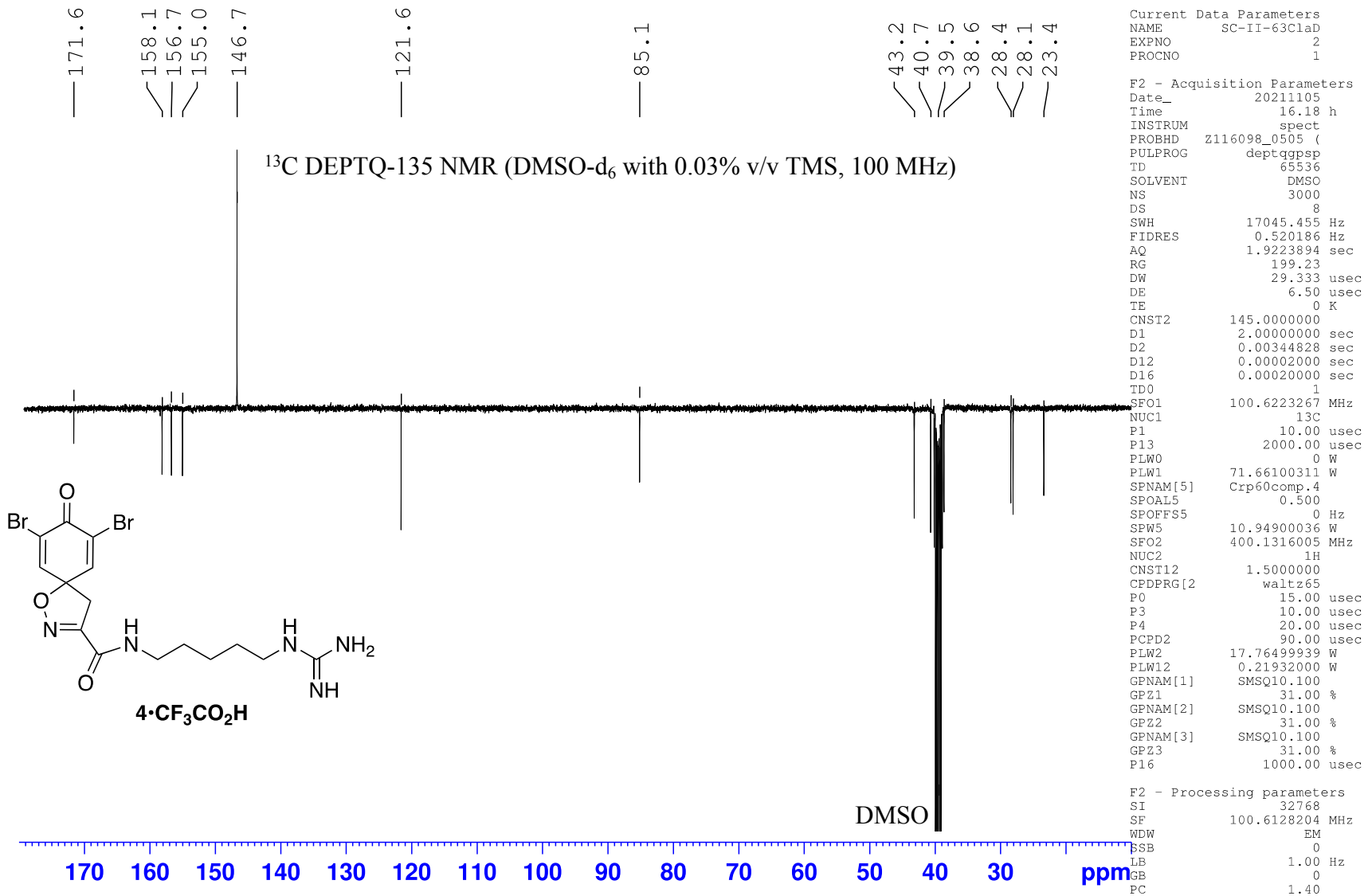

Figure S35. ^{13}C DEPTQ-135 NMR (100 MHz, DMSO-d_6) spectrum of unpurified, synthetic clavatadine D (**4**).

^{1}H-^{1}H COSY NMR (DMSO-d_6 with 0.03% v/v TMS, 400 MHz)

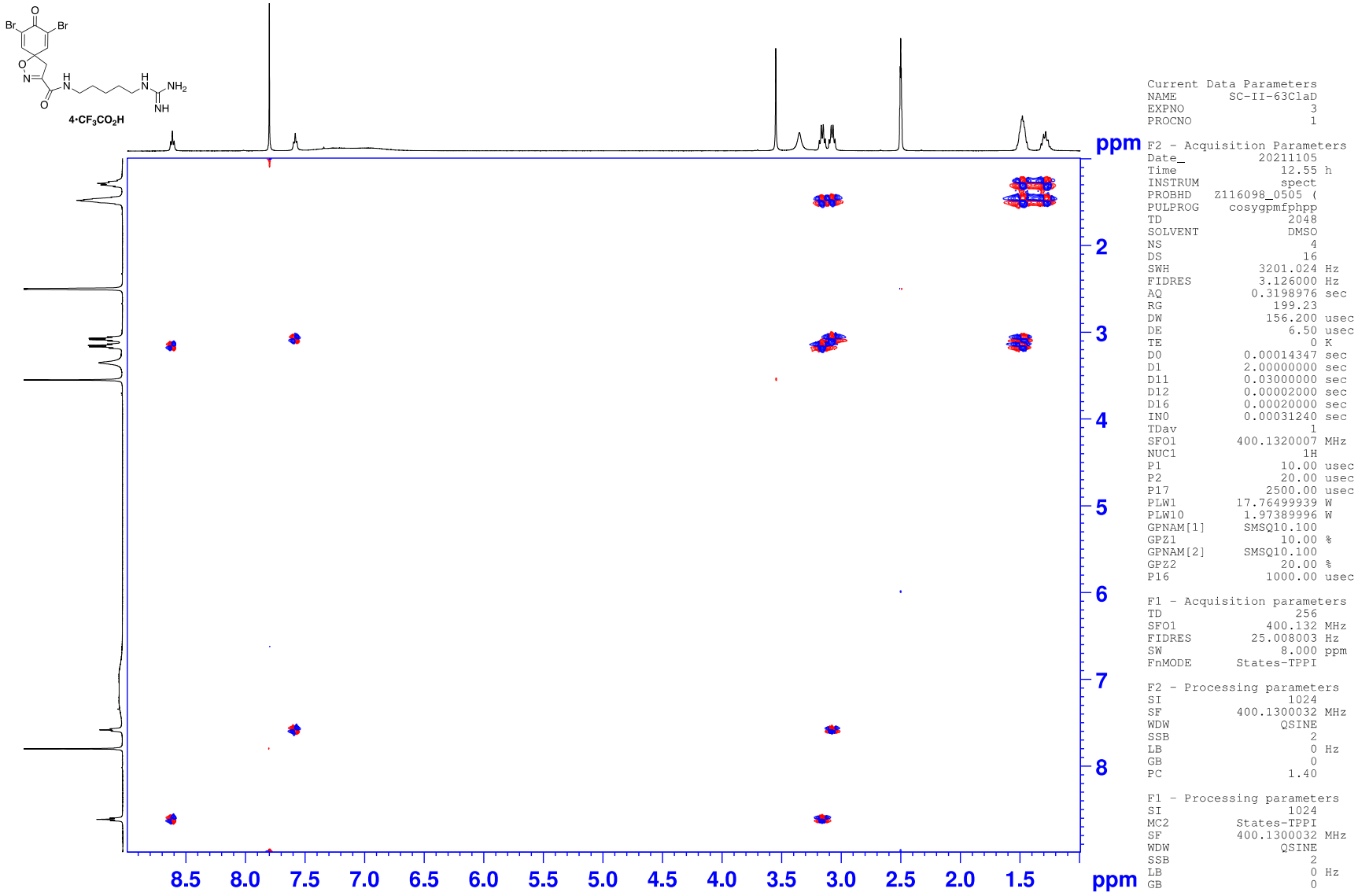

Figure S36. ^{1}H-^{1}H COSY NMR (400 MHz, DMSO-d_6) spectrum of unpurified, synthetic clavatadine D (**4**).

^{1}H-^{13}C Multiplicity-edited HSQC NMR (DMSO-d_6 with 0.03% v/v TMS, 400 MHz)

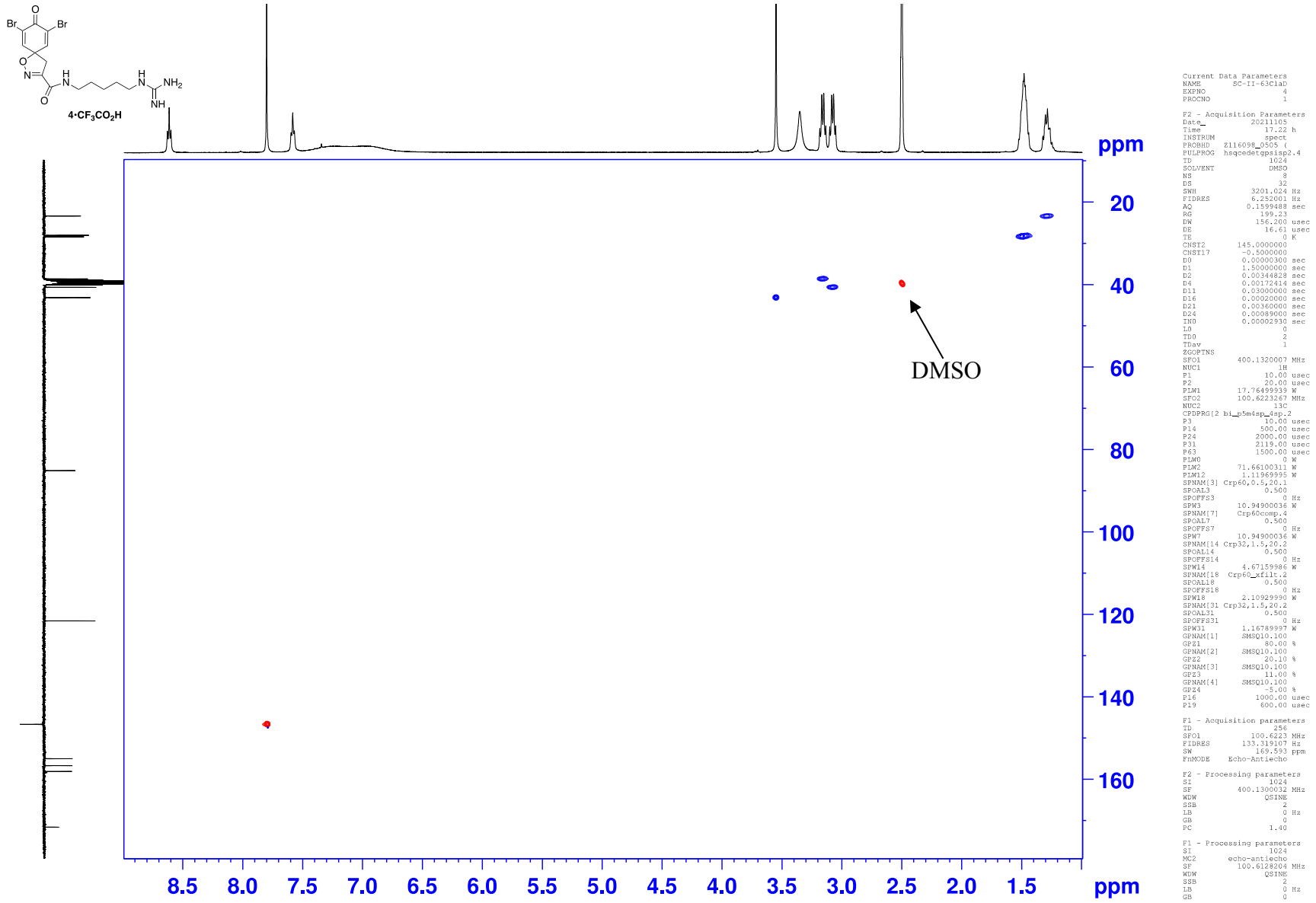

Figure S37. ^{1}H-^{13}C Multiplicity Edited HSQC NMR (400 MHz, DMSO-d_6) spectrum of unpurified, synthetic clavatadine D (**4**).

^{1}H-^{13}C HMBC NMR (DMSO-d_6 with 0.03% v/v TMS, 400 MHz)

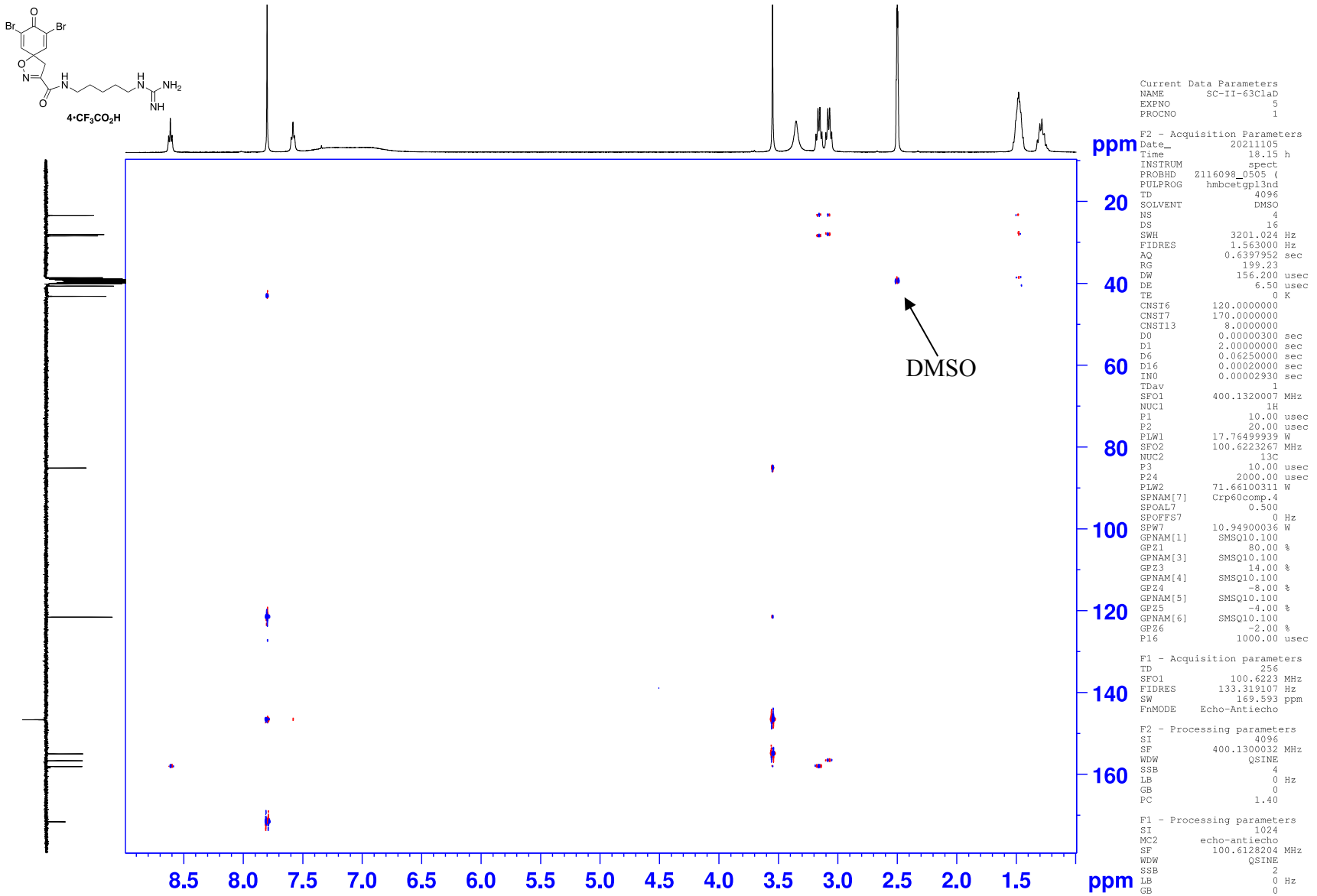

Figure S38. ^{1}H-^{13}C HMBC NMR (400 MHz, DMSO-d_6) spectrum of unpurified, synthetic clavatadine D (**4**).

Experimental details and spectra for NMR experiments on *N*,*N*-DiBoc Clavatadine C (**36**) using treated and untreated $CDCl_3$

A series of NMR experiments were performed to attempt to rationalize the discrepancy in the chemical shift of three methylene peaks found in the δ 3.3–3.6 region of the proton NMR spectrum of *N*,*N*-diBoc clavatadine C (**36**) prepared in this work and as described in the 2016 *Tetrahedron Letters* article by Hawkins and co-workers (Badart, M. P.; Squires, C. M. L.; Baird, S. K.; Hawkins, B. C. The Synthesis of Clavatadine C. *Tetrahedron Lett.* **2016**, *57* (46), 5108–5111). In each of eight separate NMR tubes, a solution was prepared using the following amounts of compound **36** dissolved in 0.6 mL of $CDCl_3$: 0.8 mg, 1.6 mg, 3.1 mg, 6.2 mg, 12.50 mg, 25.00 mg, 50.00 mg, and 100.00 mg. Attempted dissolution of 200 mg of compound **36** in 0.6 mL of $CDCl_3$ yielded a partially dissolved suspension that was not suitable for NMR analysis. The amber glass bottle that contained 100 mL of $CDCl_3$ (99.8%D, 0.03% TMS) was purchased from ThermoFisher Scientific (Item number AC20956-1000). For each NMR sample, the volume of $CDCl_3$ was measured and dispensed using a 1 mL plastic syringe equipped with a disposable 20-gauge needle. Compound **36** had been purified using column chromatography prior to NMR analysis and was determined to be free of perceptible impurities.

For these experiments, samples of compound **36** were prepared using a bottle of $CDCl_3$ that had been "treated," and also from a separate bottle that was used as received. The first set of experiments were performed using a bottle of $CDCl_3$ that had been treated upon receipt by adding enough activated 3-Angstrom molecular sieves to build a cylinder of sieves that was roughly 0.5 cm in height. The purpose of the sieves was to remove water that may have been present when the solvent was received and also water that builds up over time as the sample is periodically exposed to air. To the sieves-treated bottle was then added a small scoop of solid potassium carbonate, which was designed to remove any HCl or DCl that may form if the chloroform degrades upon exposure to ambient light. Both the treated and untreated bottles were stored on the laboratory bench and were capped securely but were not sealed further, such as with Parafilm. ^{1}H NMR spectra (ambient temperature, 16 scans, 2 dummy scans, standard processing) were collected on the same day the samples were prepared (time-zero = "T0") and approximately 24 hours later (T0 + one day = "T1"). The purpose of the time delay between data collections was to probe whether compound **36** underwent degradation in a solution of $CDCl_3$ that was left at ambient temperature. All spectra were standardized to the residual chloroform signal at δ 7.270. It was preferable to standardize spectra to TMS; however, TMS evaporated from solutions within a day after preparation and thus could not be used as a reference.[2]

What follows are the ^{1}H NMR spectra acquired on compound **36** in order of increasing concentration using treated chloroform on the day of preparation, treated chloroform 24 h after preparation, untreated chloroform on the day of preparation, and untreated chloroform 24 h after preparation. The chemical shift of each peak was reported as the tallest peak in each grouping in cases where splitting occurred or the peak itself for a singlet. When overlapping occurred in the ^{1}H spectrum and the chemical shift of peaks could not be cleanly discerned, chemical shift values were determined and confirmed using the following two-dimensional NMR experiments: a multiplicity-edited HSQC (pulse sequence hsqcedetgpsisp2.4) followed by a higher-resolution band-selective 2D HSQC (shsqcetgpsisp2.2). Chemical shift values were further verified using 2-D NOESY (pulse sequence noesygpphpp). Both sets of 2D experiments were collected approximately 2-3 weeks after initial sample preparation.

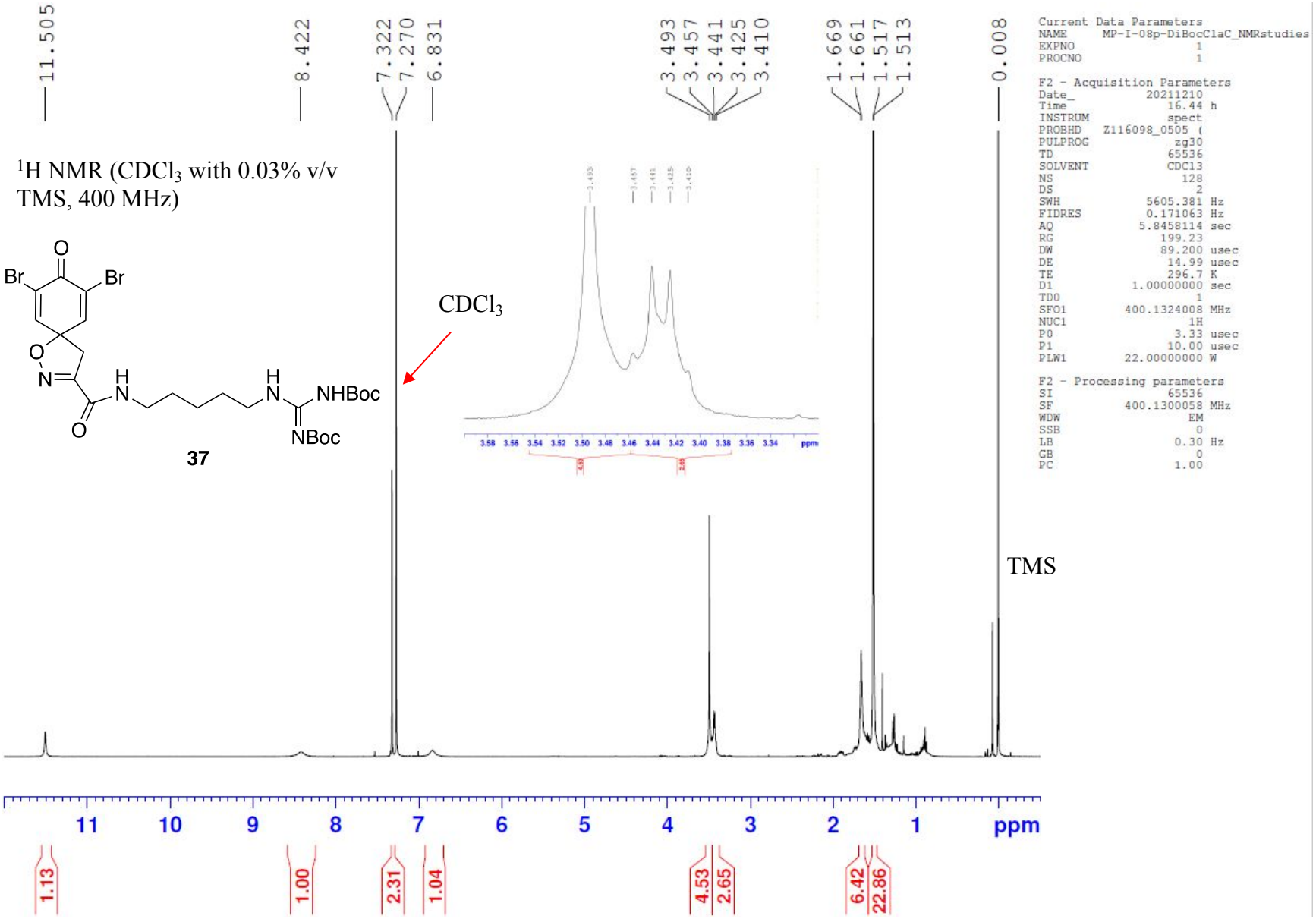

Figure S39. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 0.8 mg of known compound (**36**) in 0.6 mL of treated $CDCl_3$, T0.

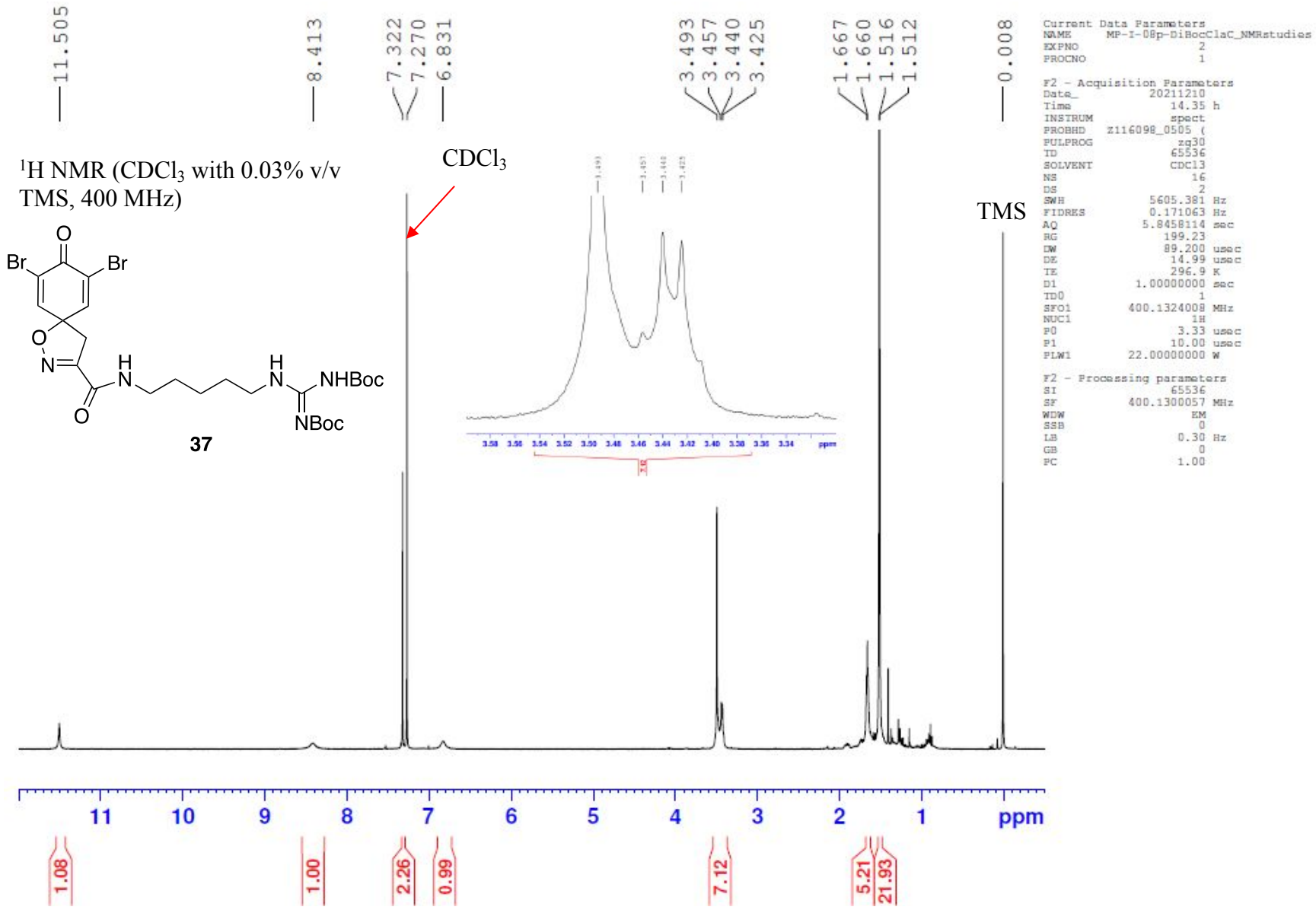

Figure S40. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 1.6 mg of known compound (**36**) in 0.6 mL of treated $CDCl_3$, T0.

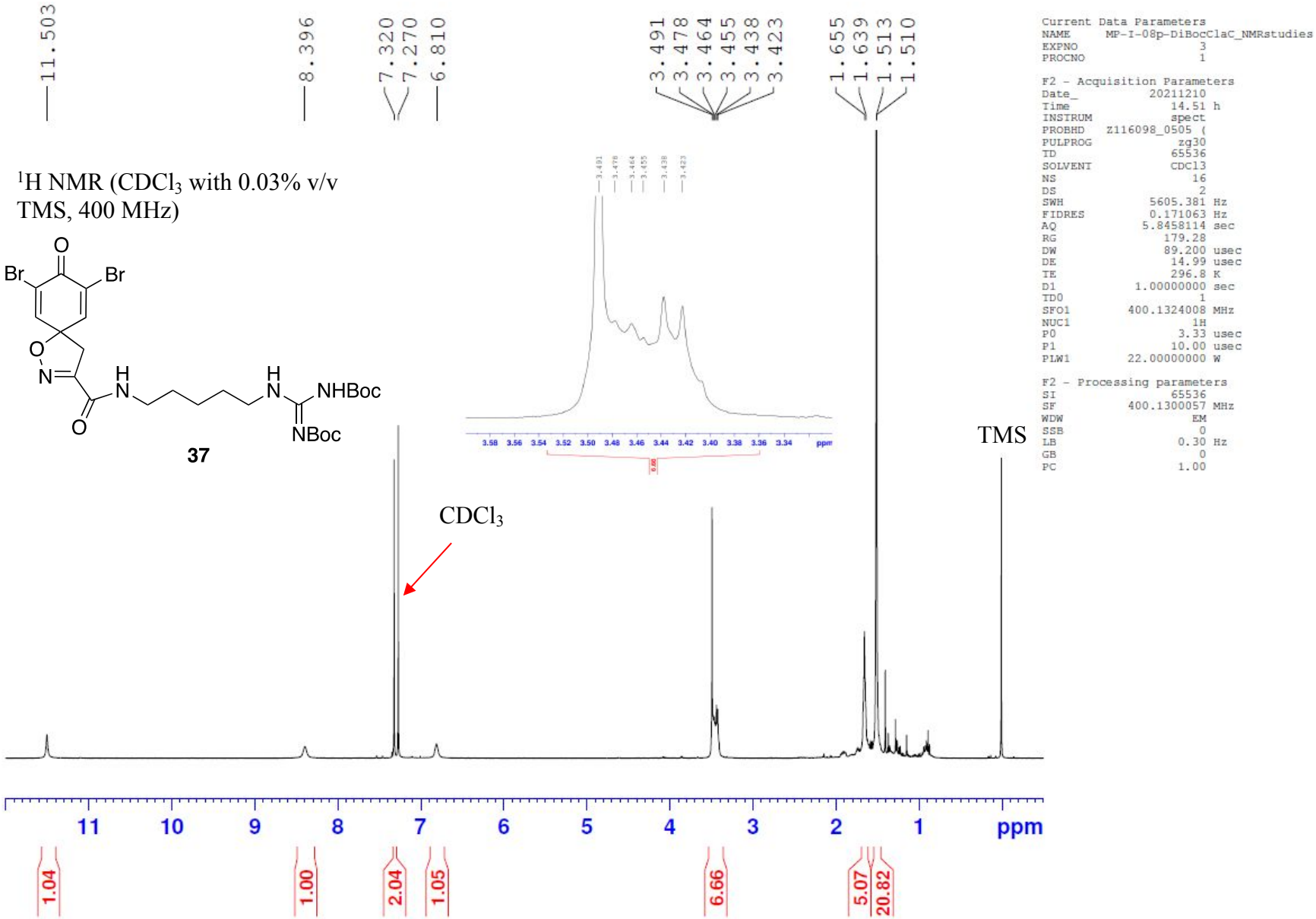

Figure S41. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3.1 mg of known compound (**36**) in 0.6 mL of treated $CDCl_3$, T0.

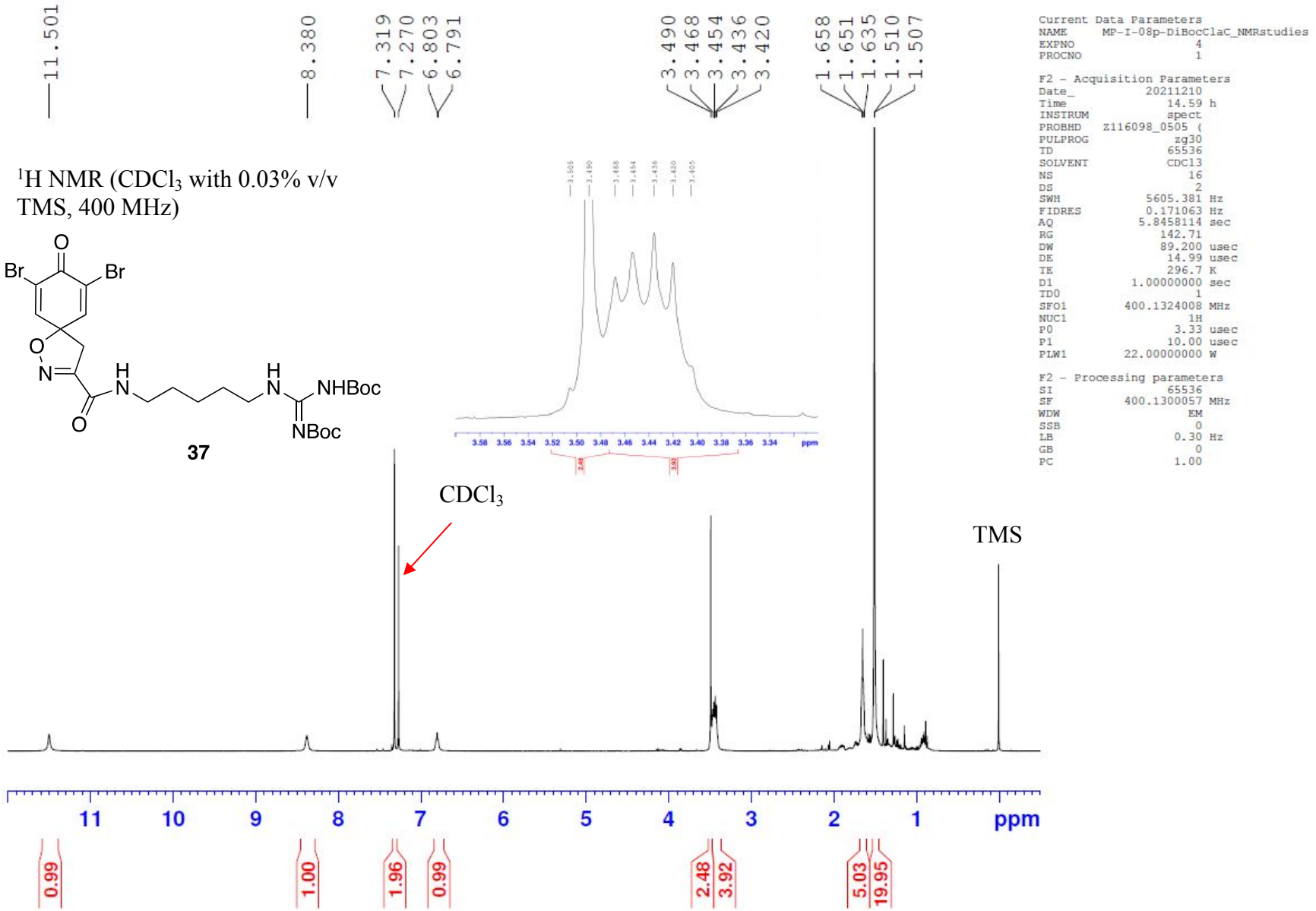

Figure S42. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 6.2 mg of known compound (**36**) in 0.6 mL of treated $CDCl_3$, T0.

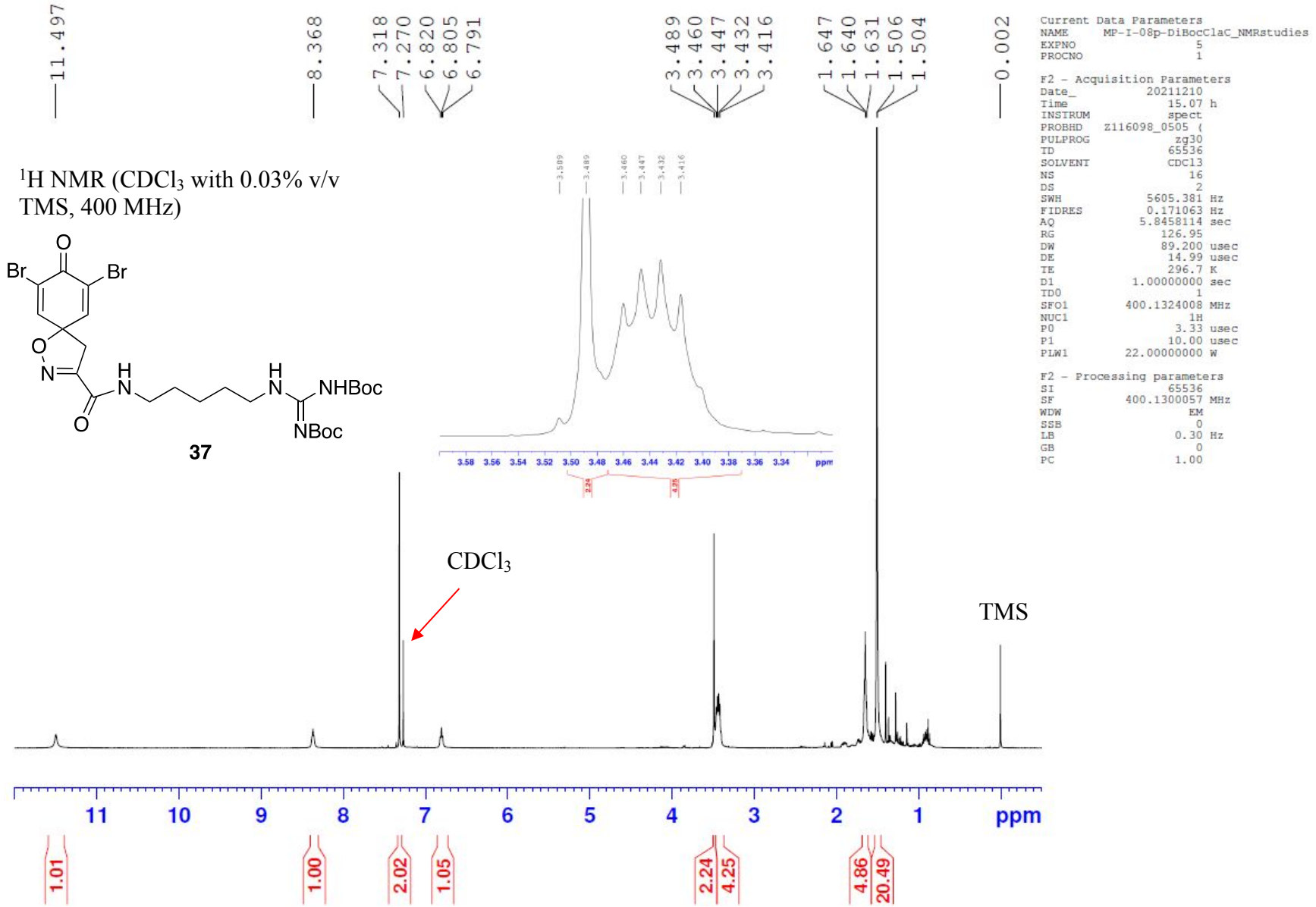

Figure S43. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 12.5 mg of known compound (**36**) in 0.6 mL of treated $CDCl_3$, T0.

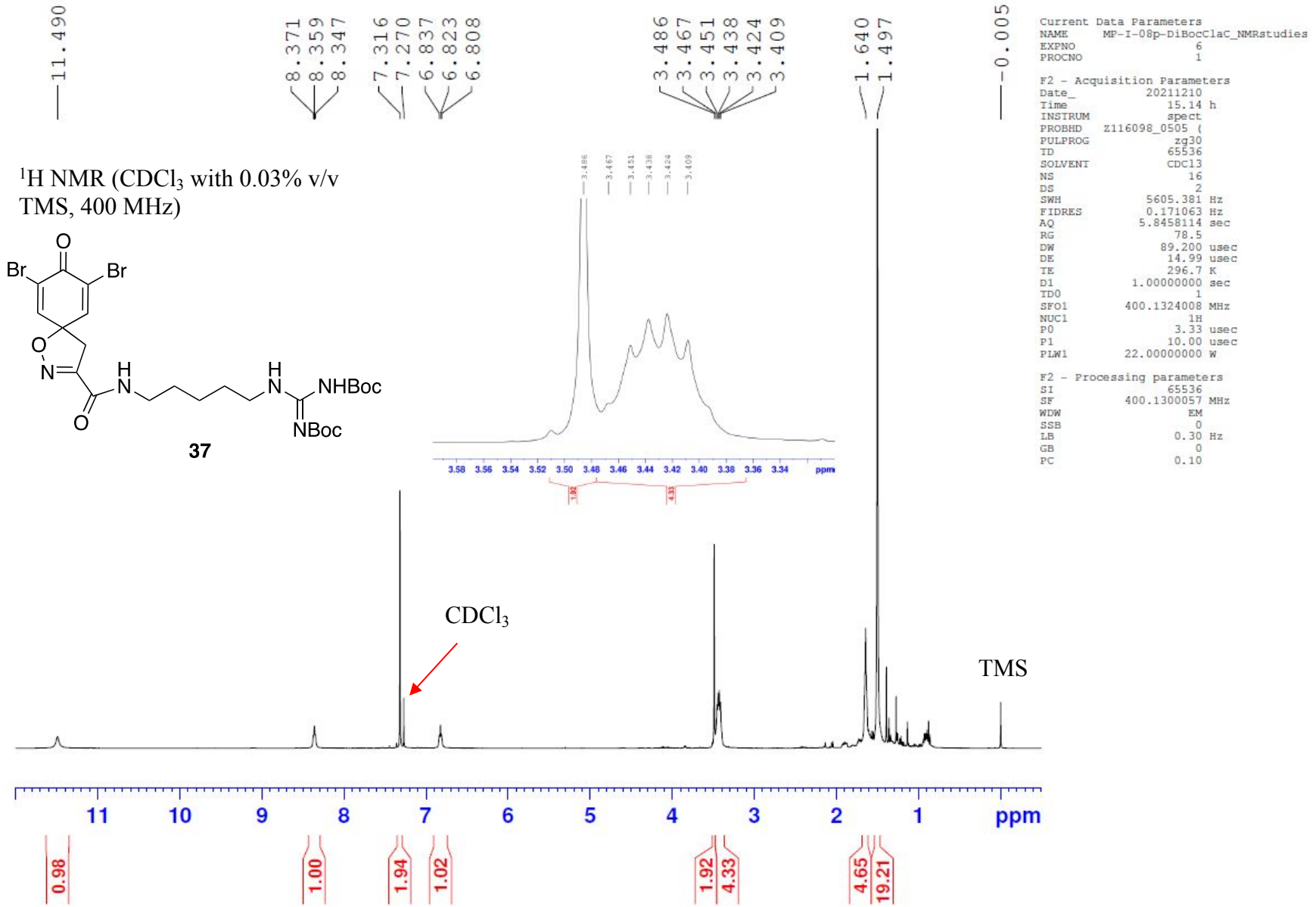

Figure S44. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 25 mg of known compound (**36**) in 0.6 mL of treated $CDCl_3$, T0.

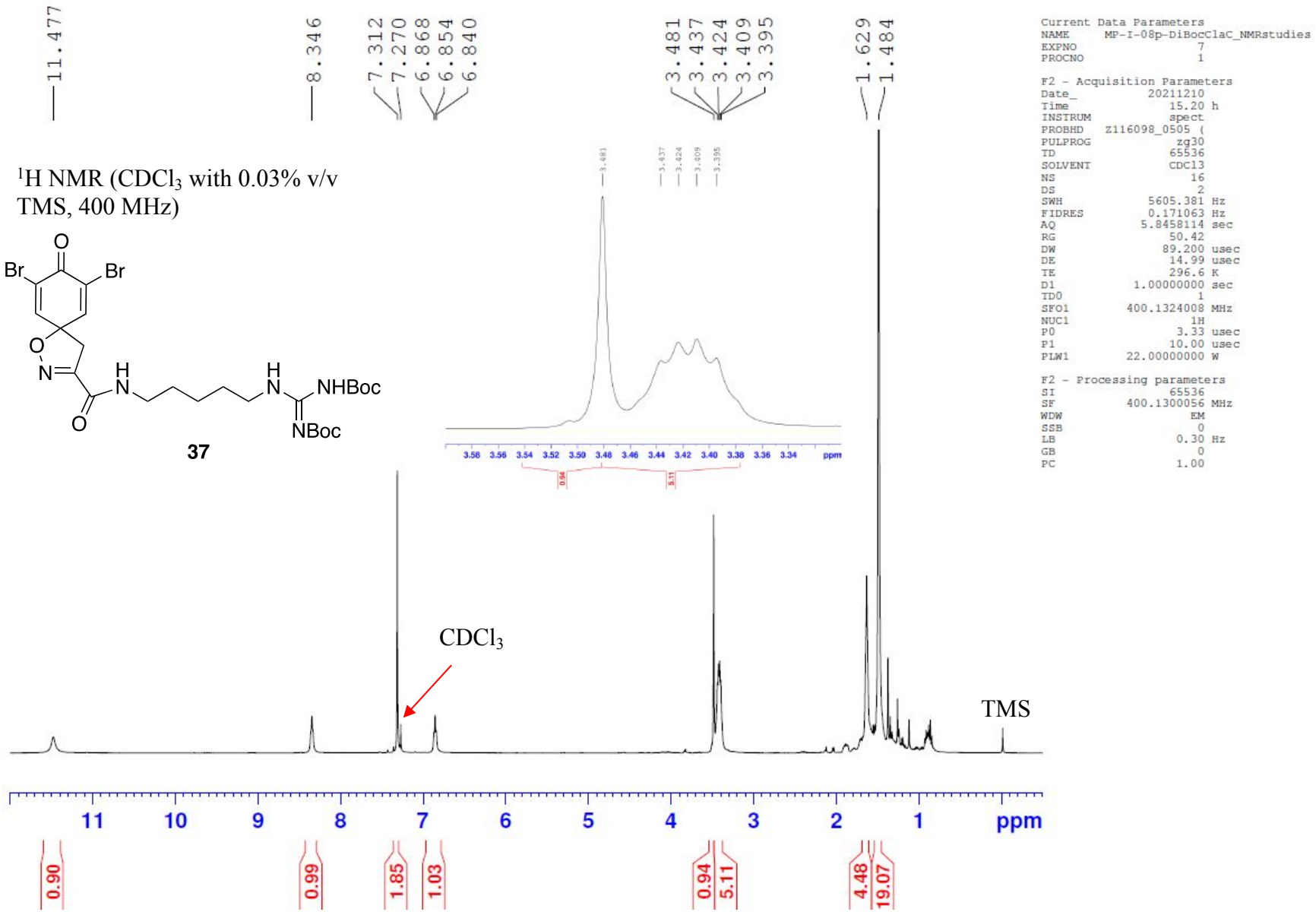

Figure S45. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 50 mg of known compound (**36**) in 0.6 mL of treated $CDCl_3$, T0.

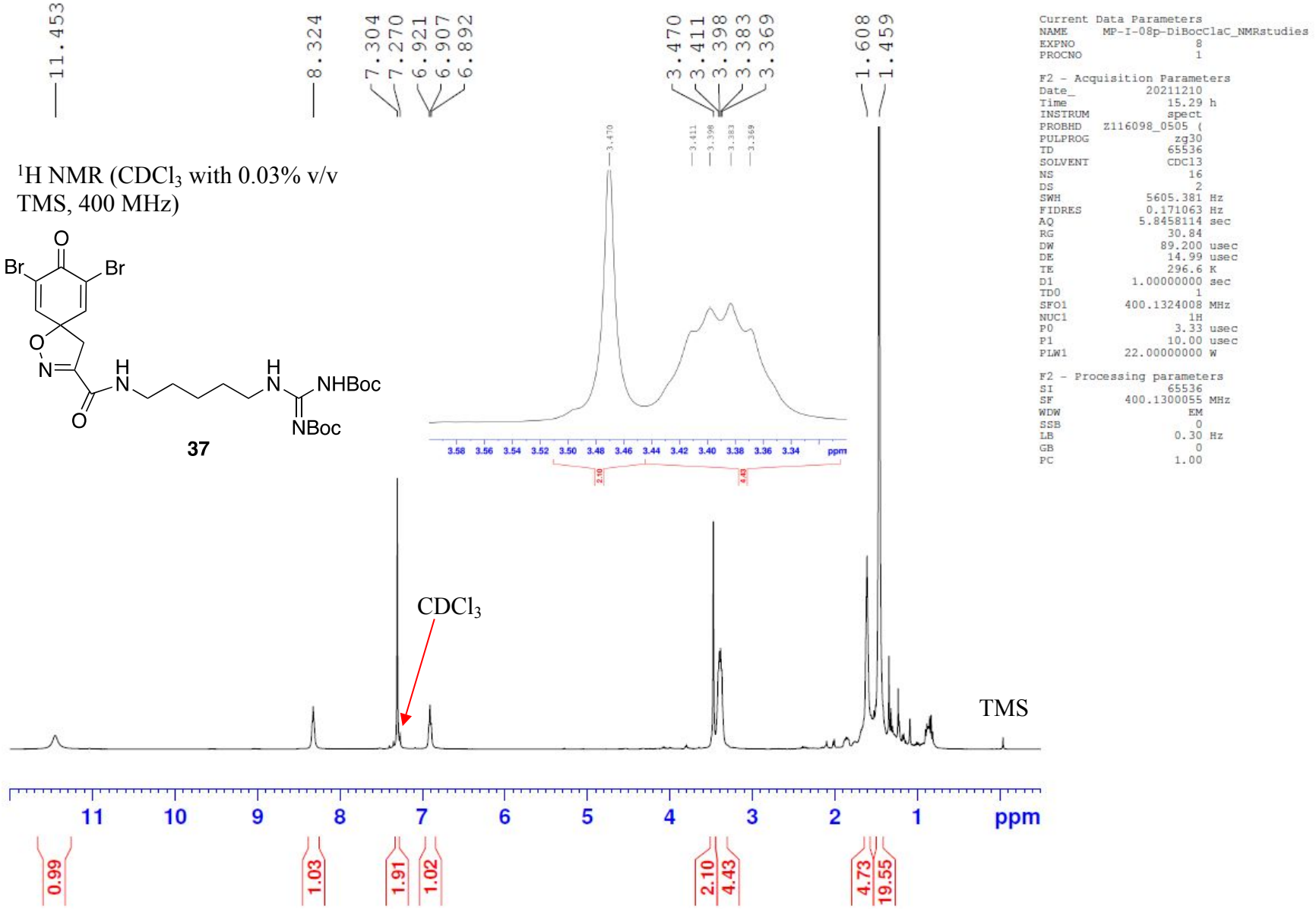

Figure S46. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 100 mg of known compound (**36**) in 0.6 mL of treated $CDCl_3$, T0.

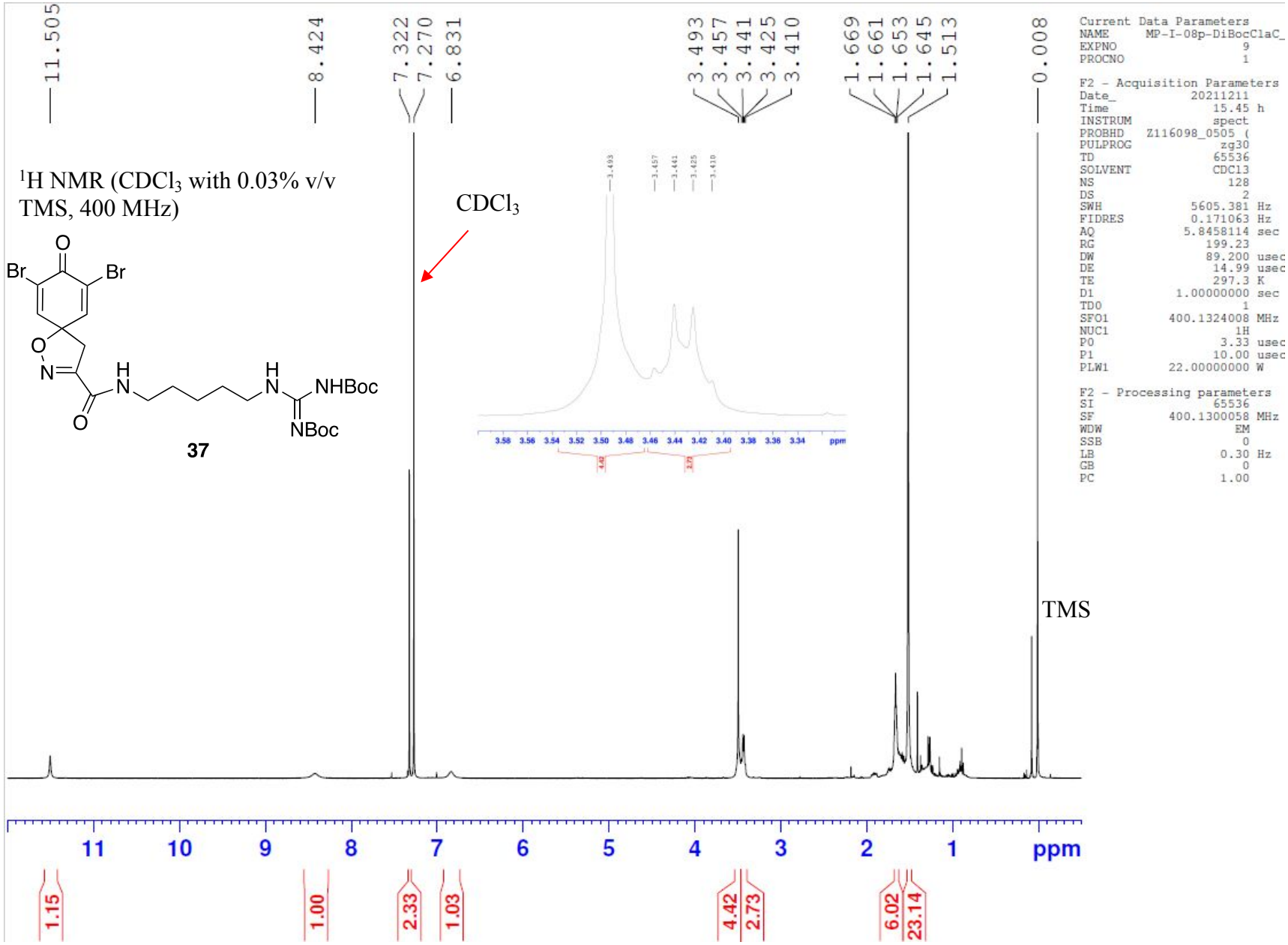

Figure S47. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 0.8 mg of known compound (**36**) in 0.6 mL of treated $CDCl_3$, T1.

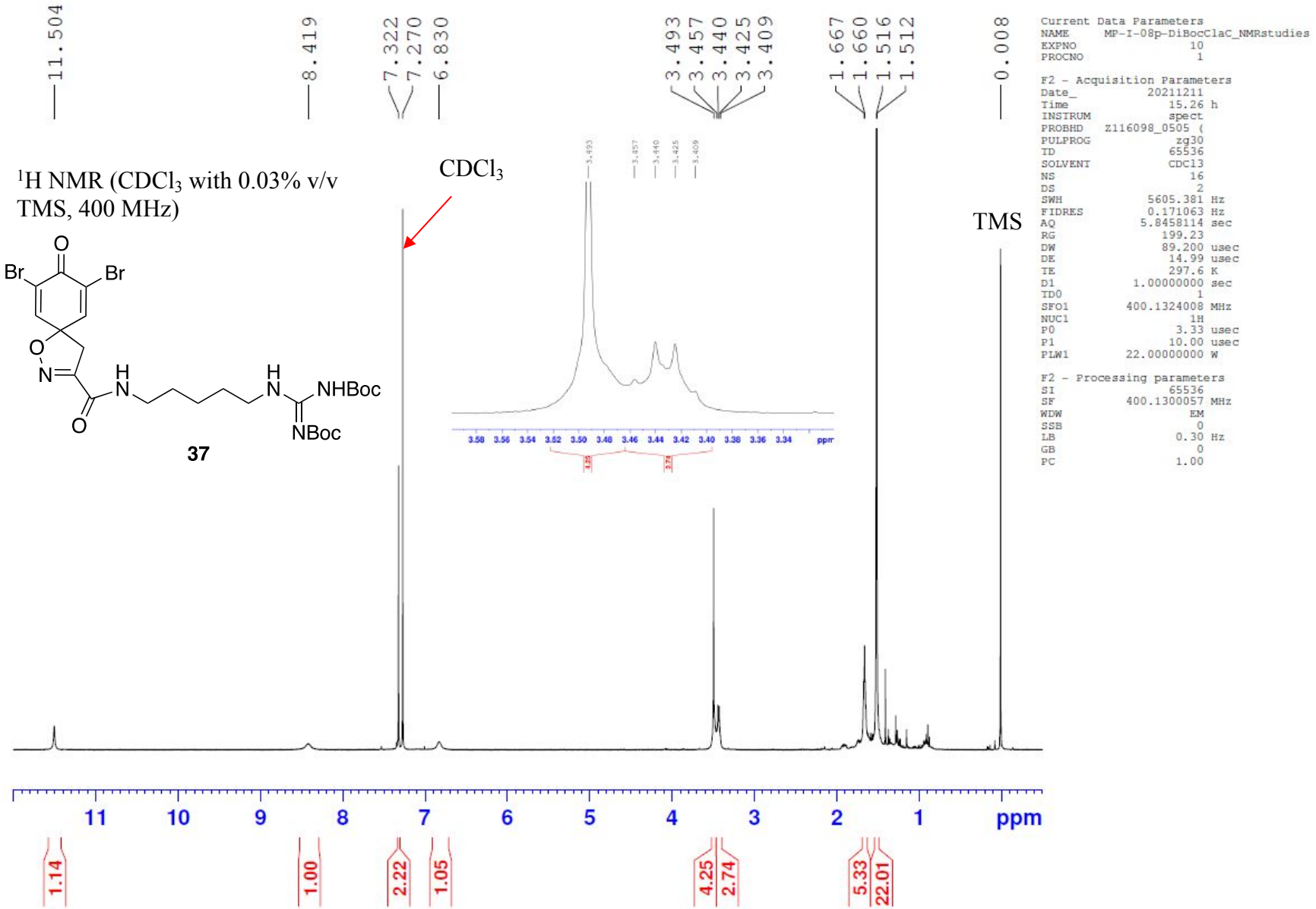

Figure S48. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 1.6 mg of known compound (**36**) in 0.6 mL of treated $CDCl_3$, T1.

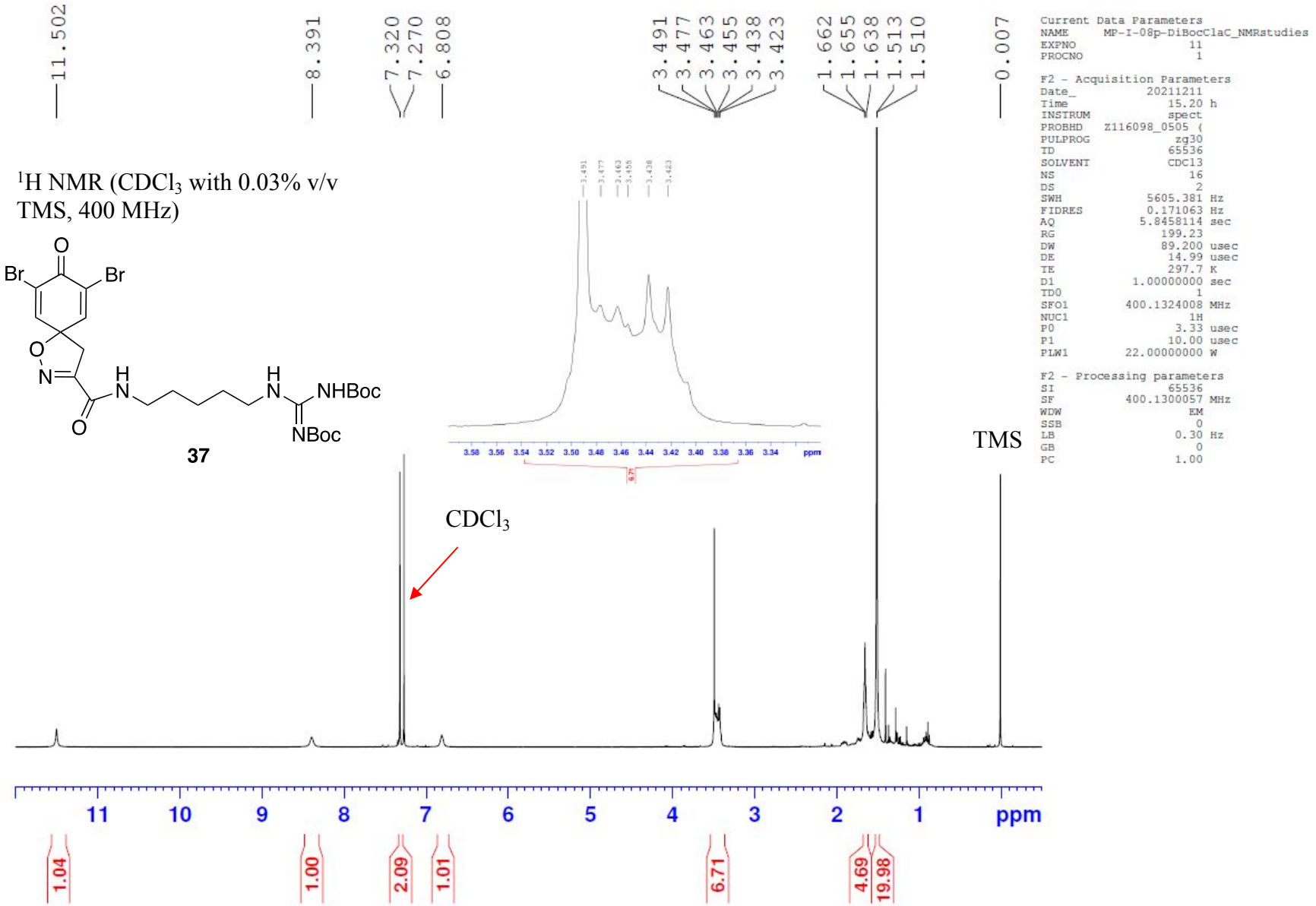

Figure S49. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3.1 mg of known compound (**36**) in 0.6 mL of treated $CDCl_3$, T1.

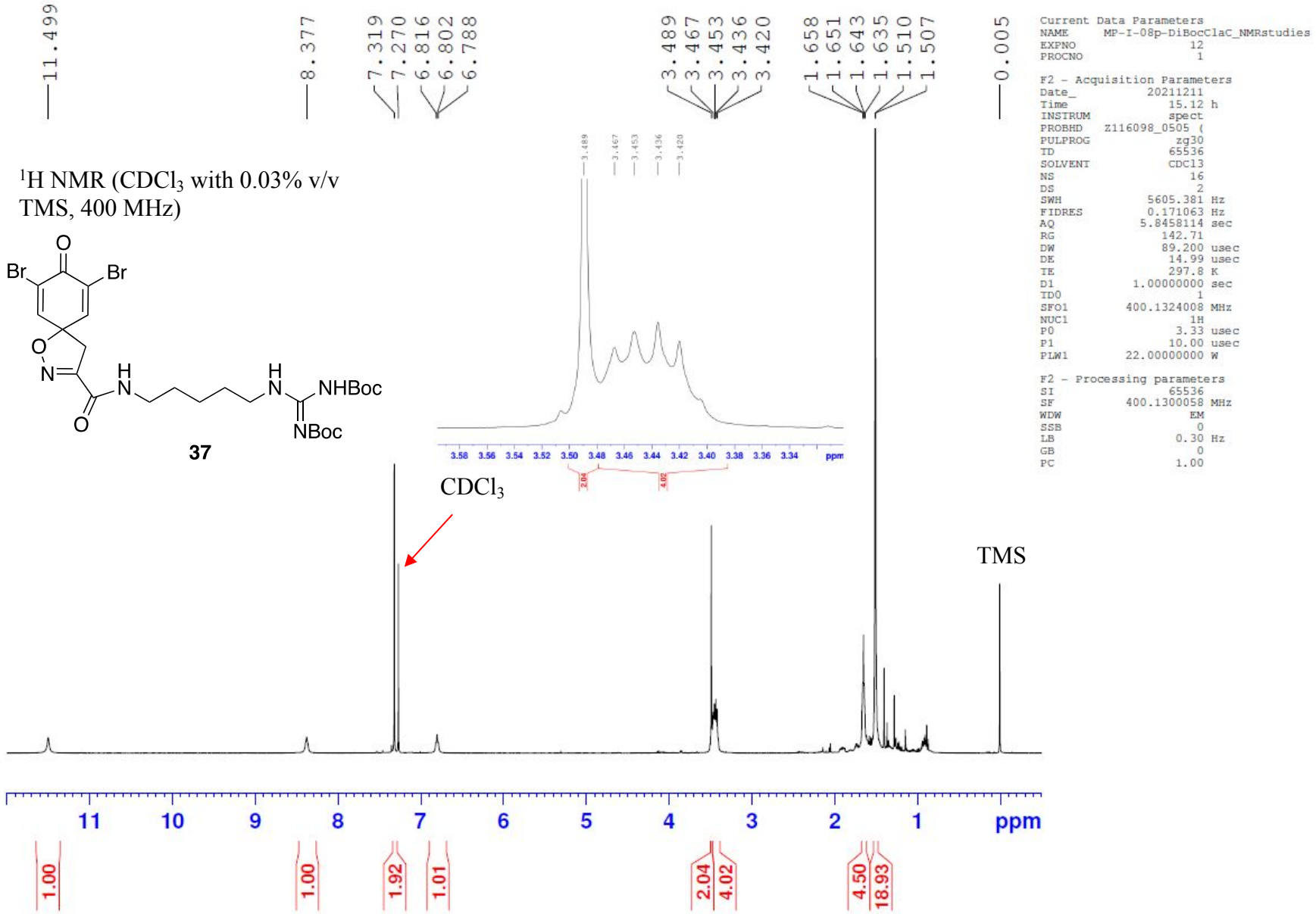

Figure S50. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 6.2 mg of known compound (**36**) in 0.6 mL of treated $CDCl_3$, T1.

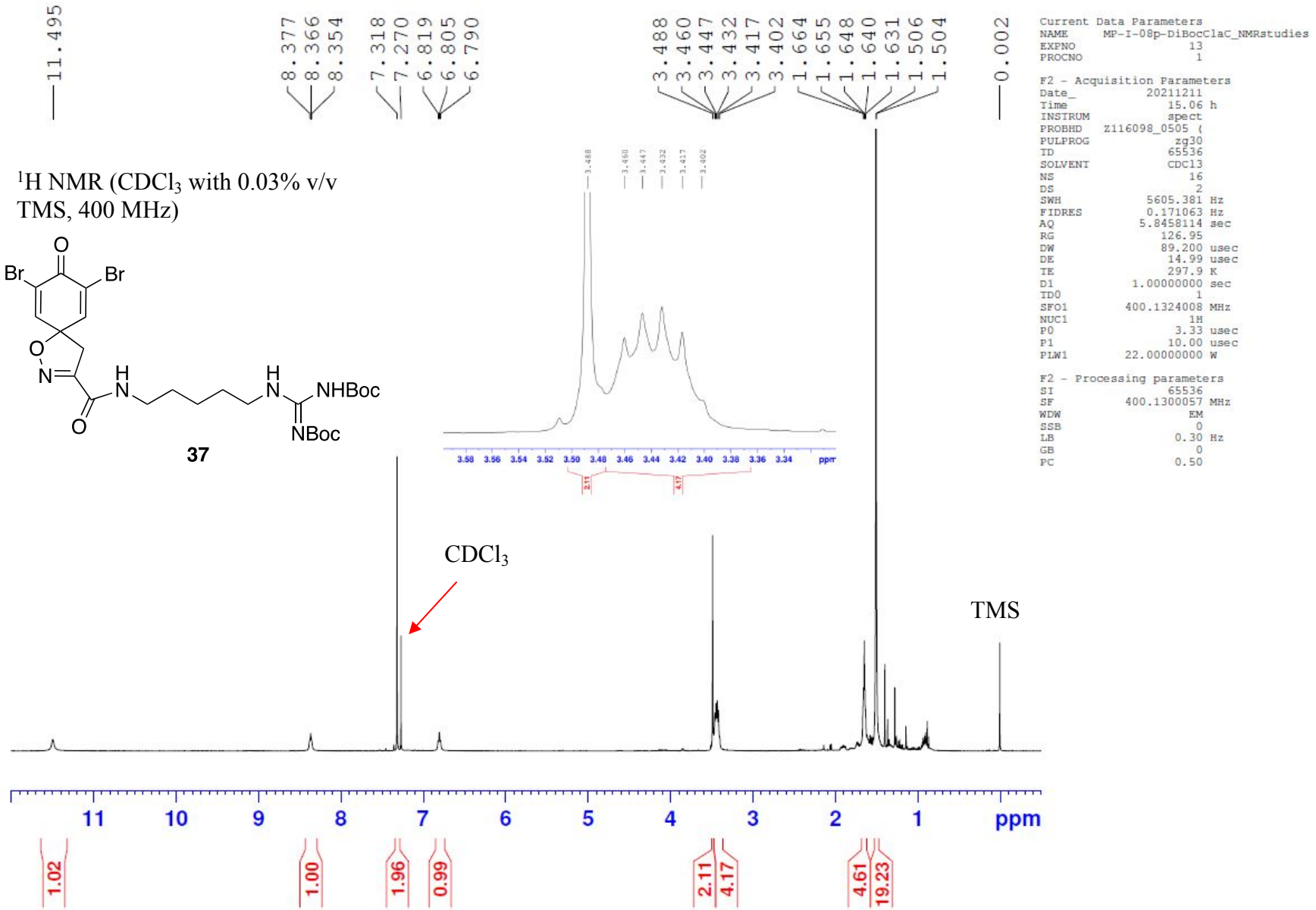

Figure S51. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 12.5 mg of known compound (**36**) in 0.6 mL of treated $CDCl_3$, T1.

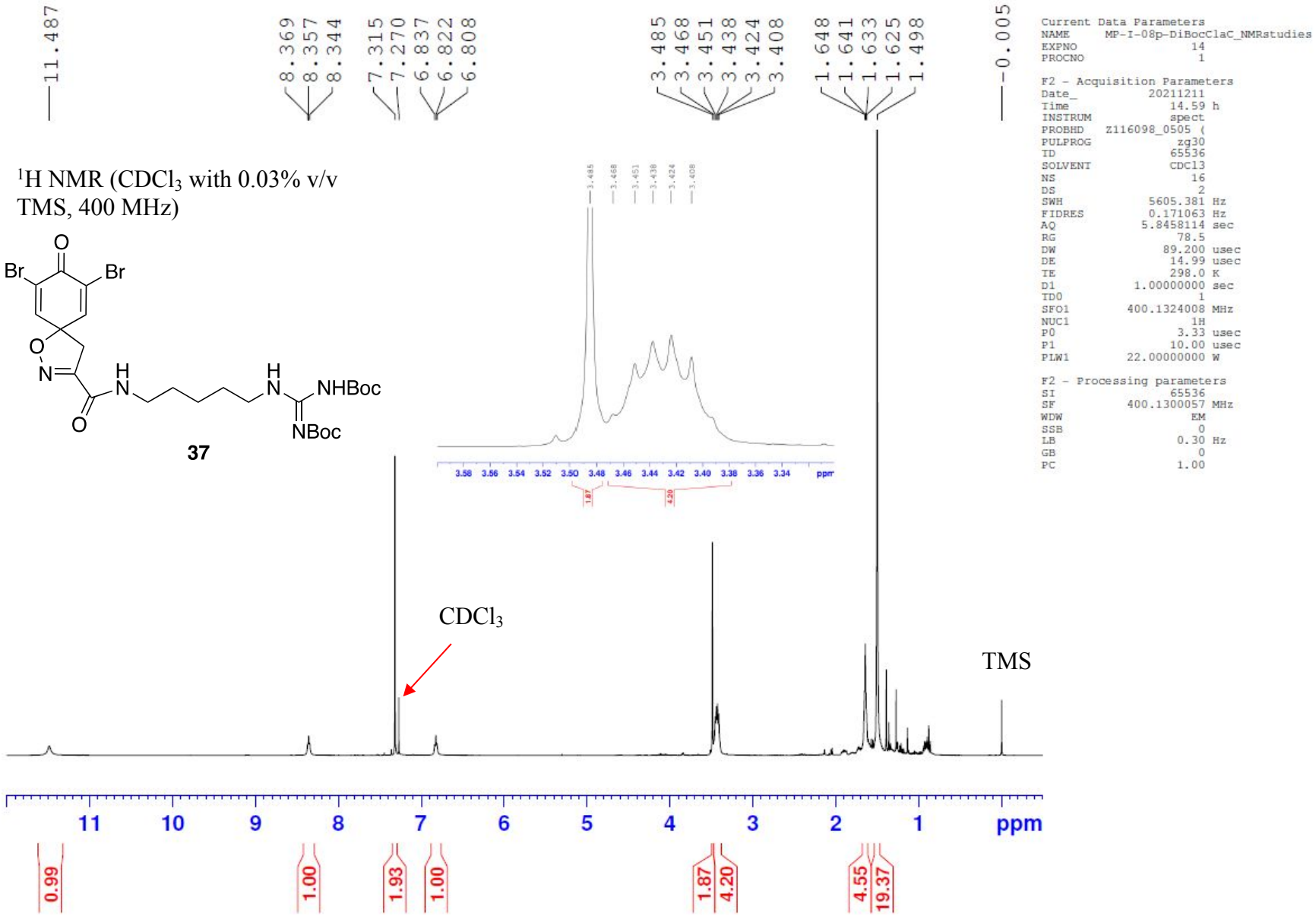

Figure S52. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 25 mg of known compound (**36**) in 0.6 mL of treated $CDCl_3$, T1.

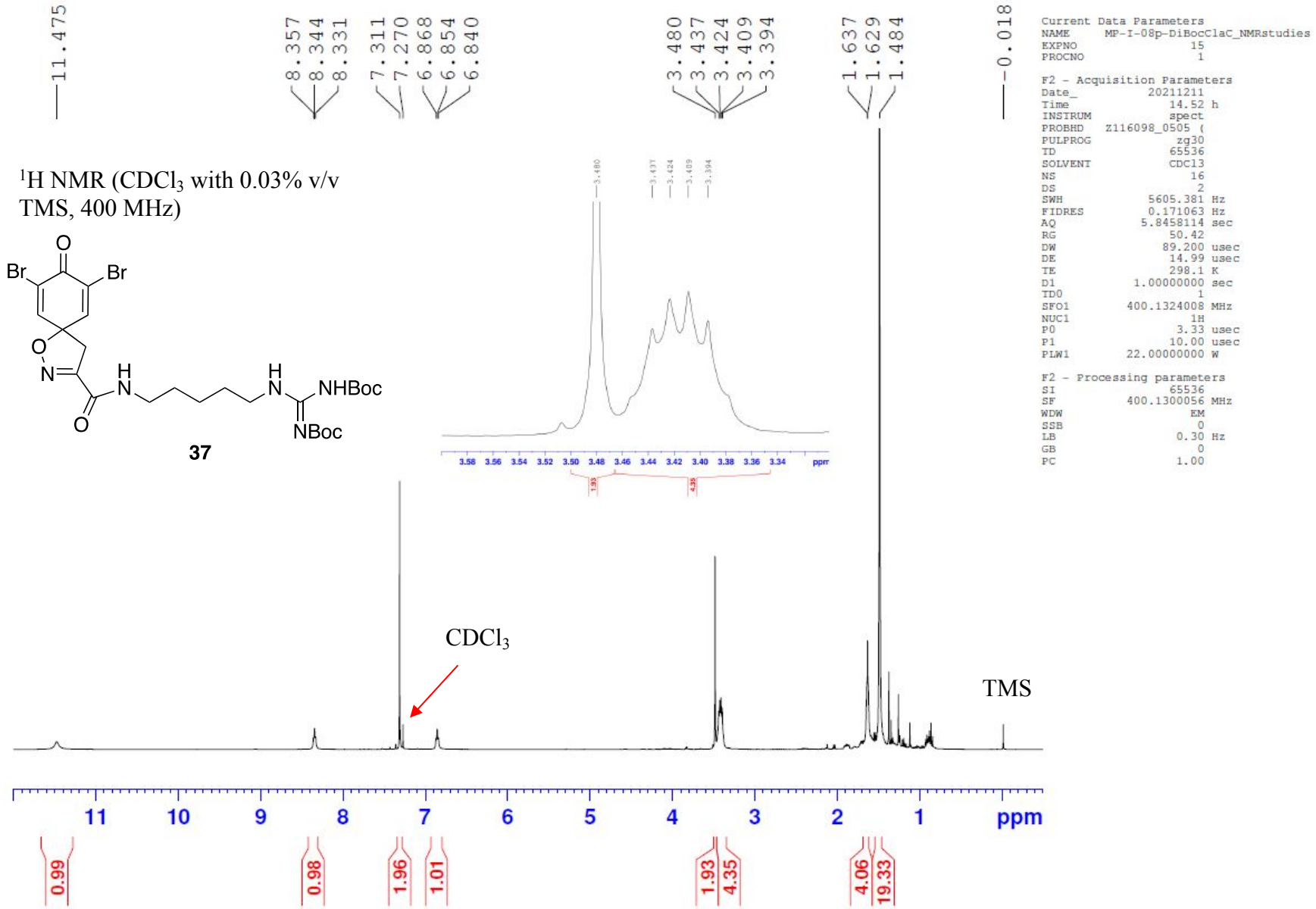

Figure S53. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 50 mg of known compound (**36**) in 0.6 mL of treated $CDCl_3$, T1.

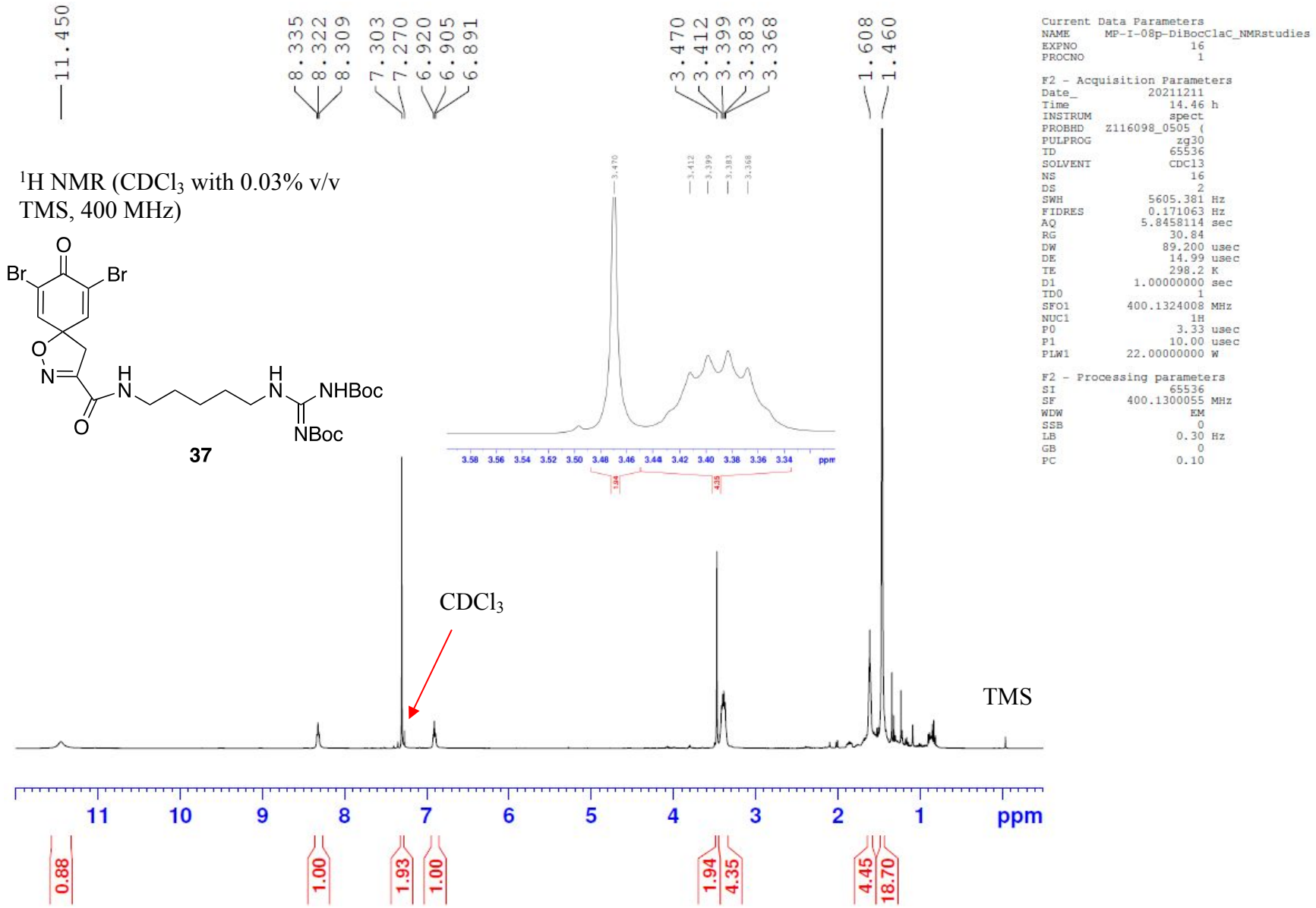

Figure S54. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 100 mg of known compound (**36**) in 0.6 mL of treated $CDCl_3$, T1.

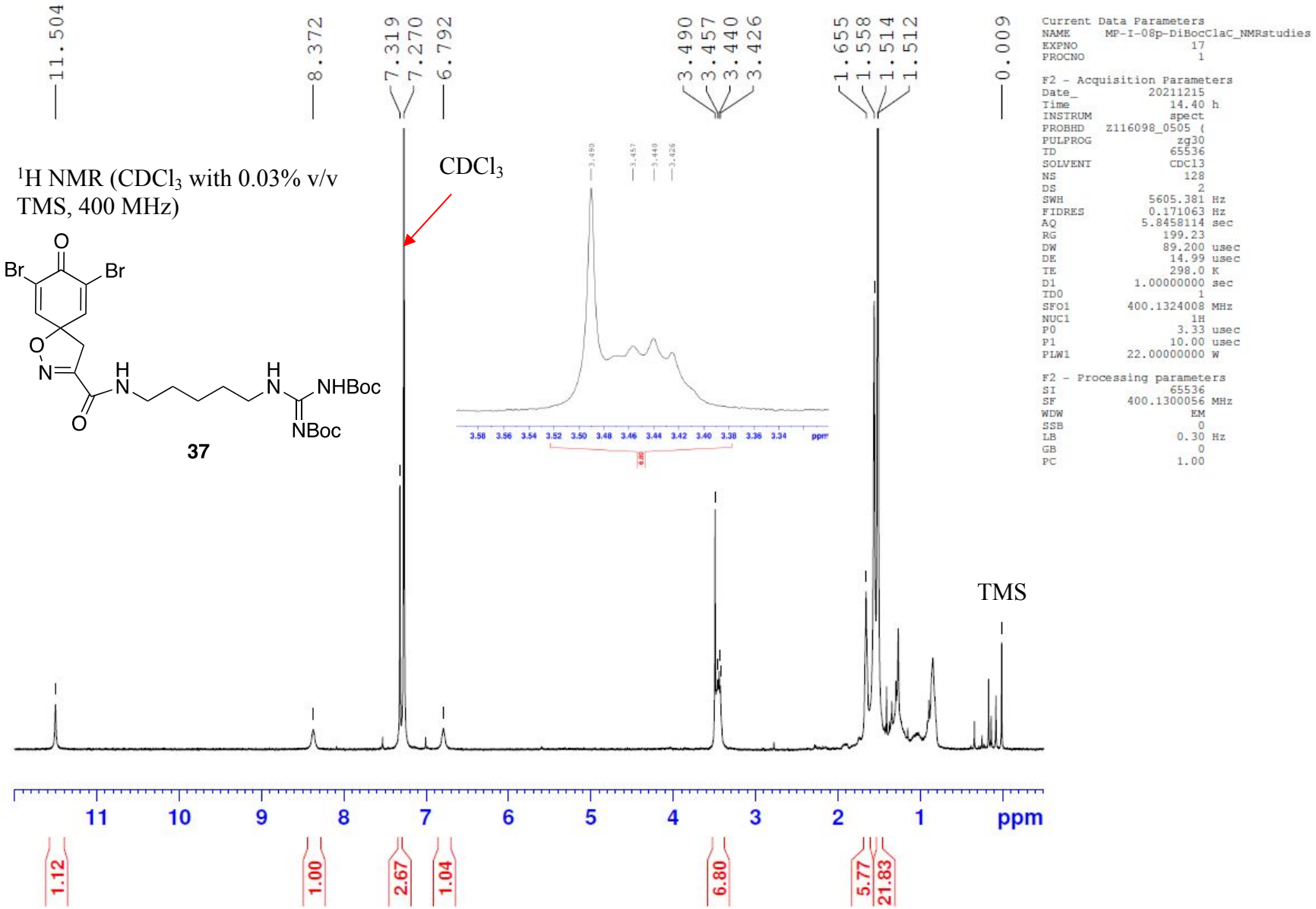

Figure S55. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 0.8 mg of known compound (**36**) in 0.6 mL of untreated $CDCl_3$, T0.

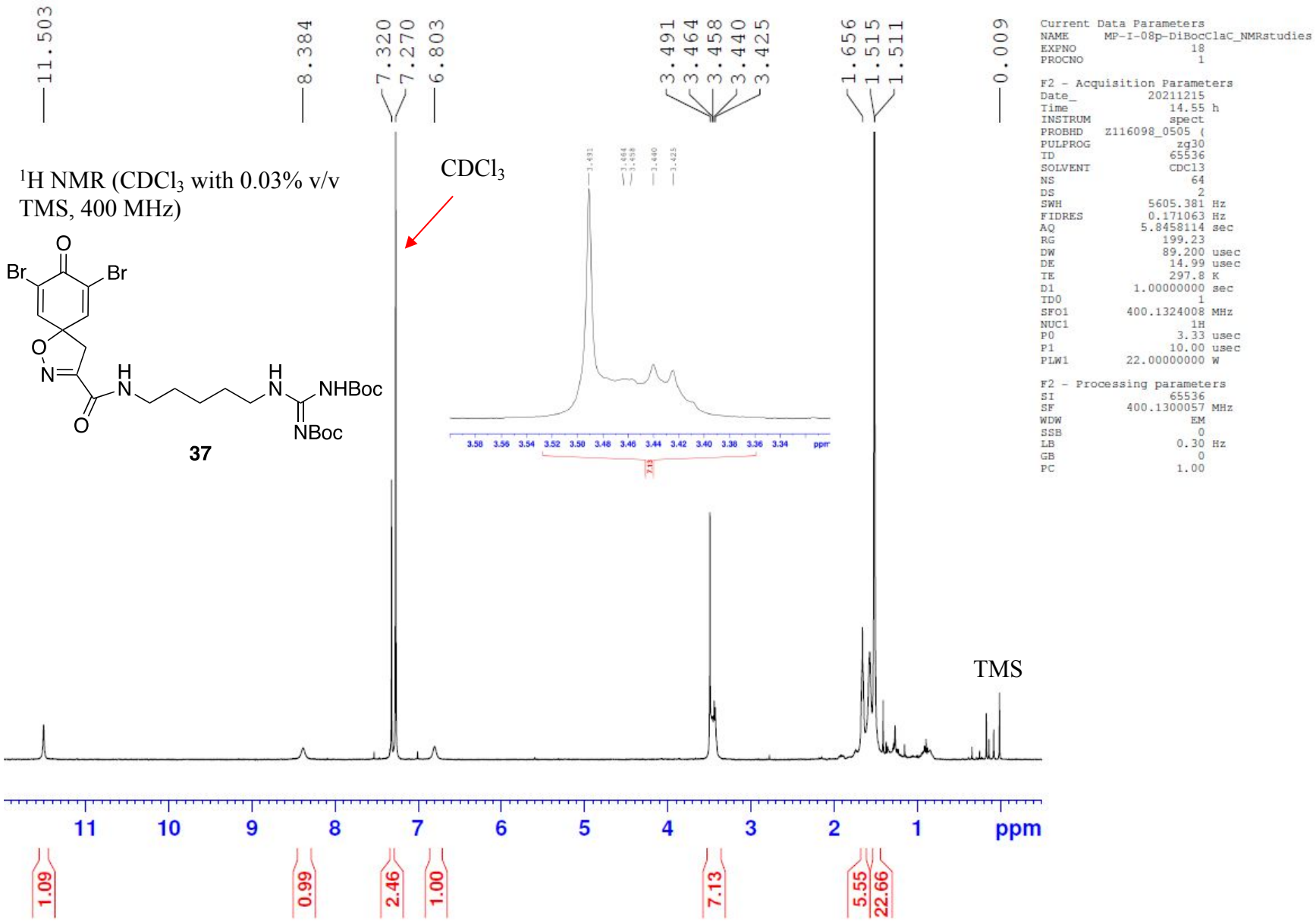

Figure S56. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 1.6 mg of known compound (**36**) in 0.6 mL of untreated $CDCl_3$, T0.

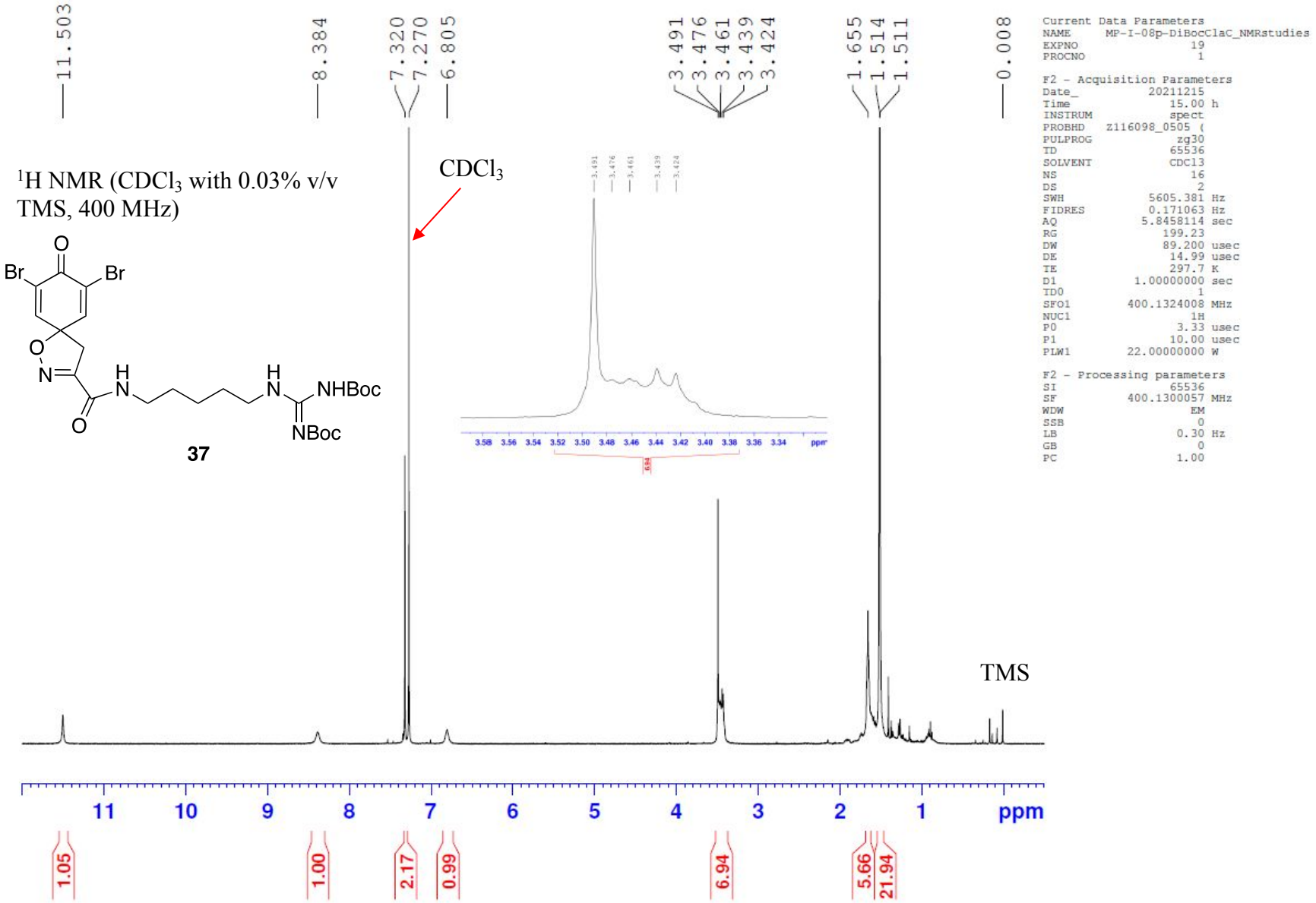

Figure S57. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3.1 mg of known compound (**36**) in 0.6 mL of untreated $CDCl_3$, T0.

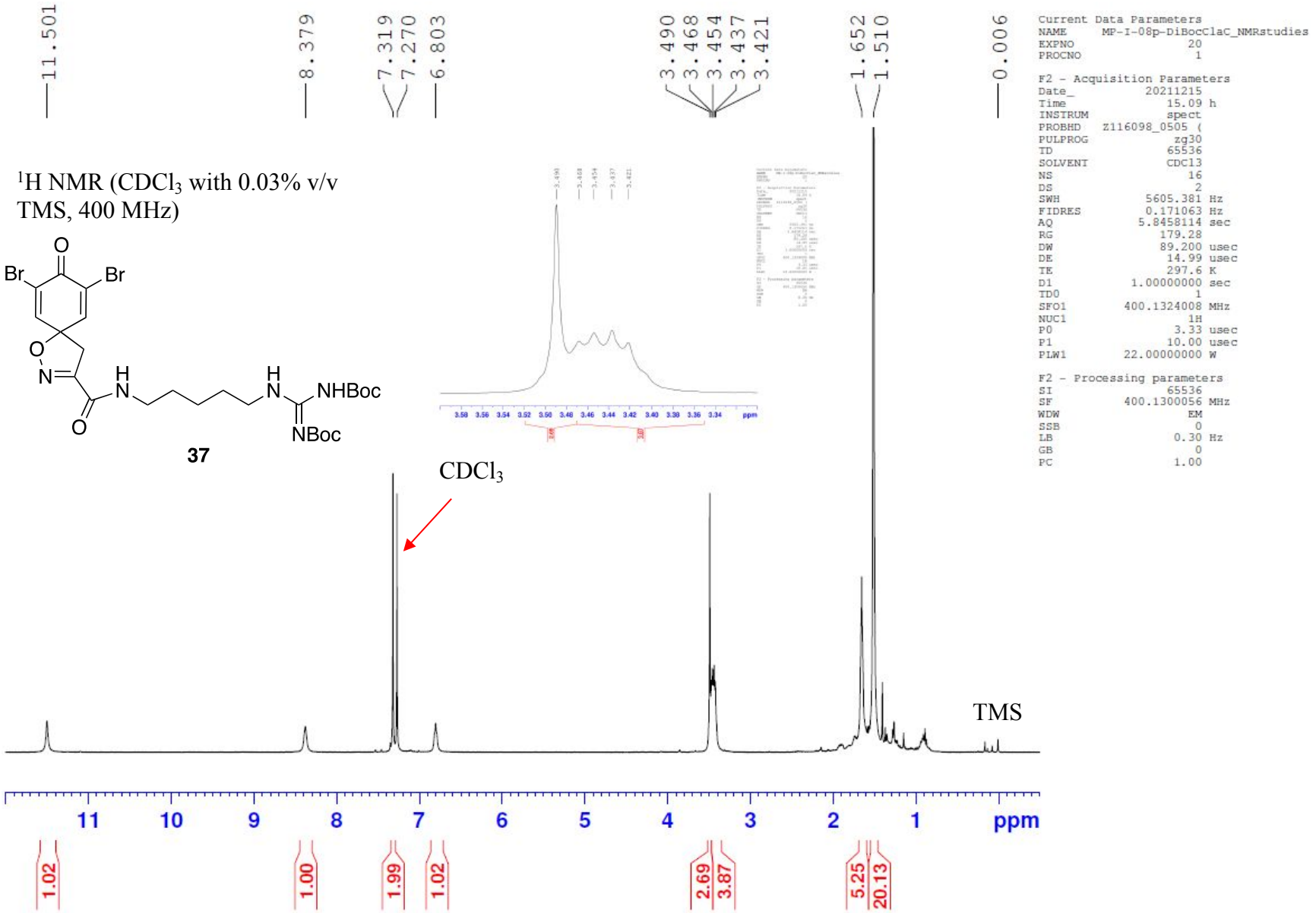

Figure S58. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 6.2 mg of known compound (**36**) in 0.6 mL of untreated $CDCl_3$, T0.

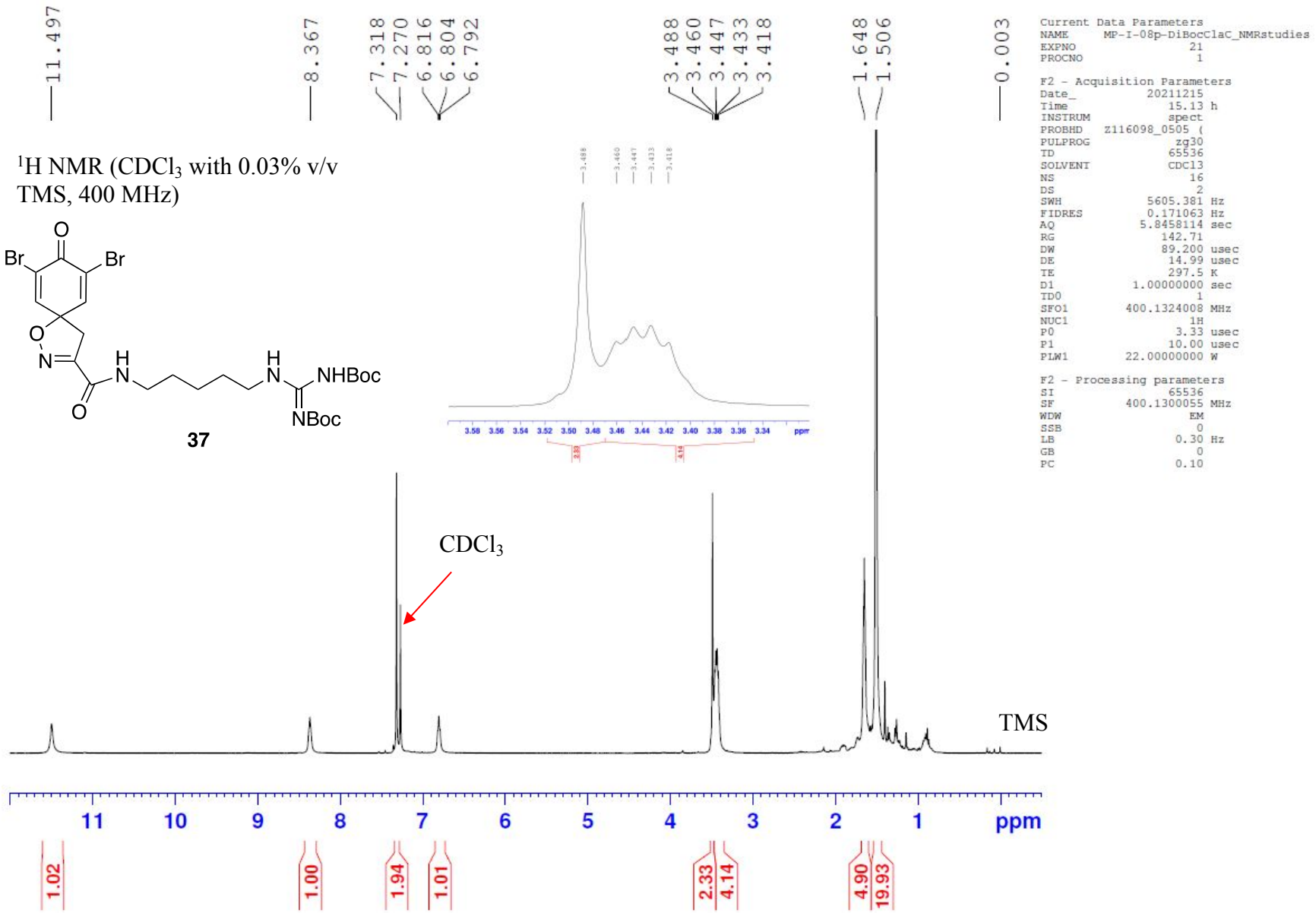

Figure S59. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 12.5 mg of known compound (**36**) in 0.6 mL of untreated $CDCl_3$, T0.

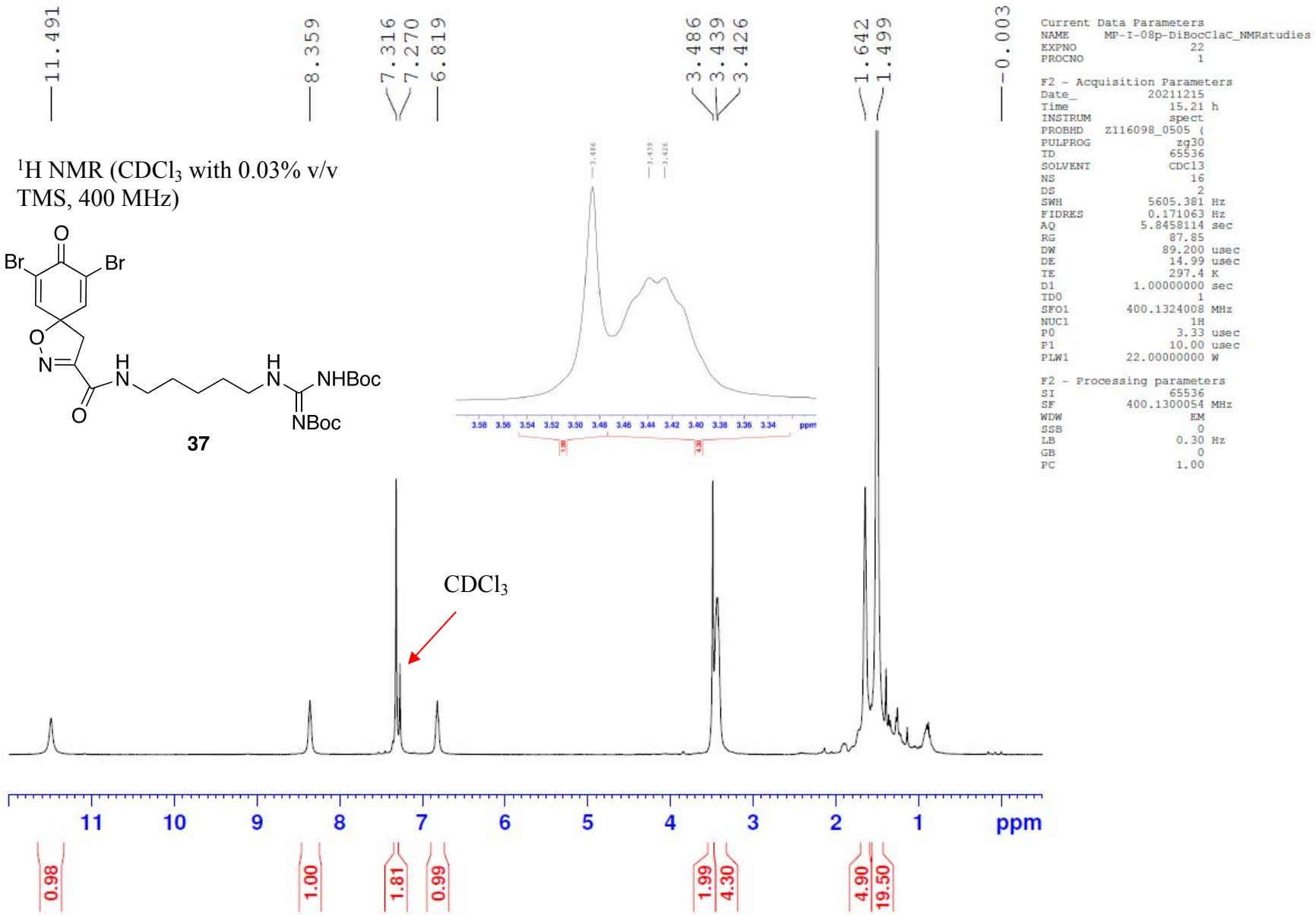

Figure S60. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 25 mg of known compound (**36**) in 0.6 mL of untreated $CDCl_3$, T0.

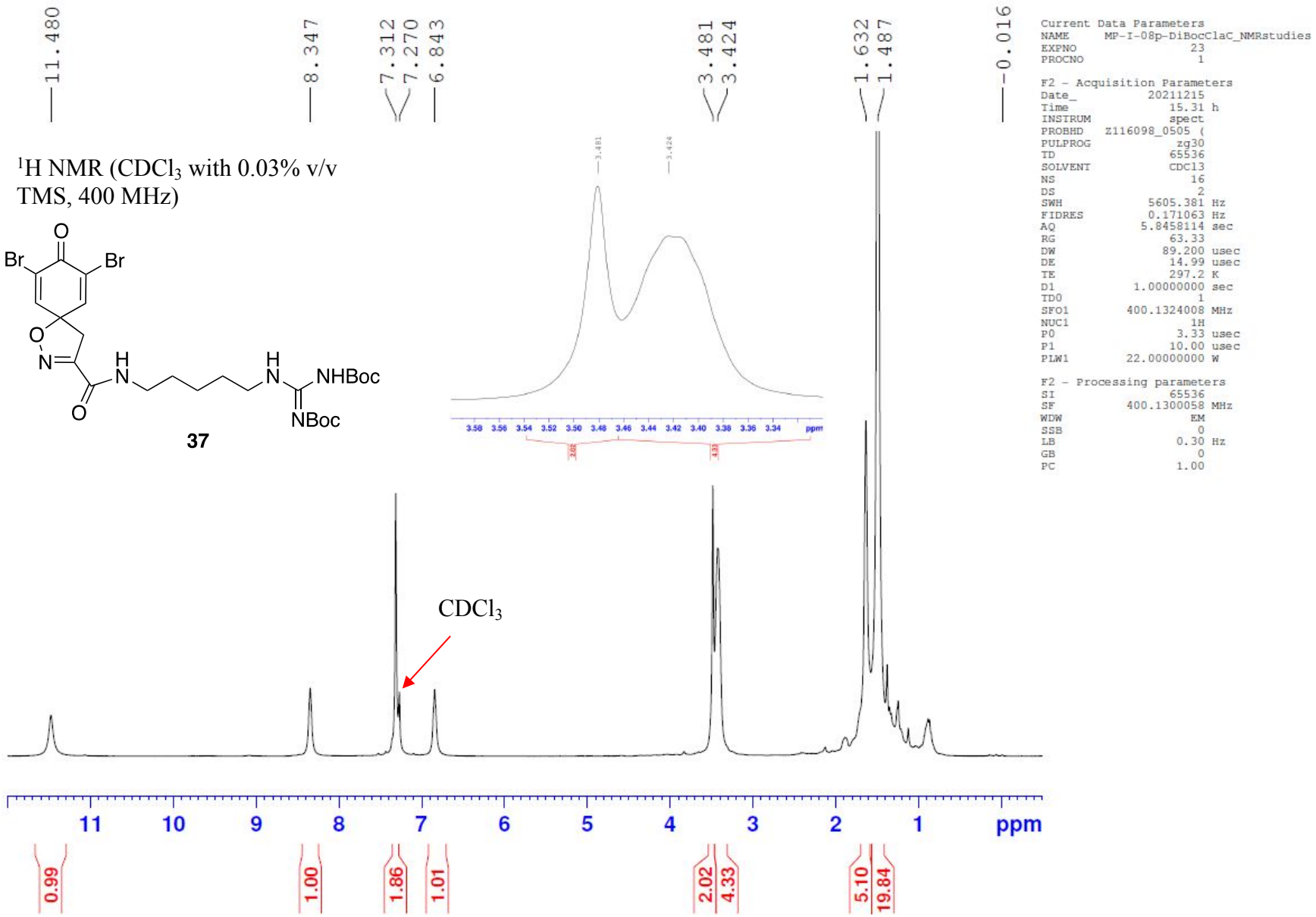

Figure S61. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 50 mg of known compound (**36**) in 0.6 mL of untreated $CDCl_3$, T0.

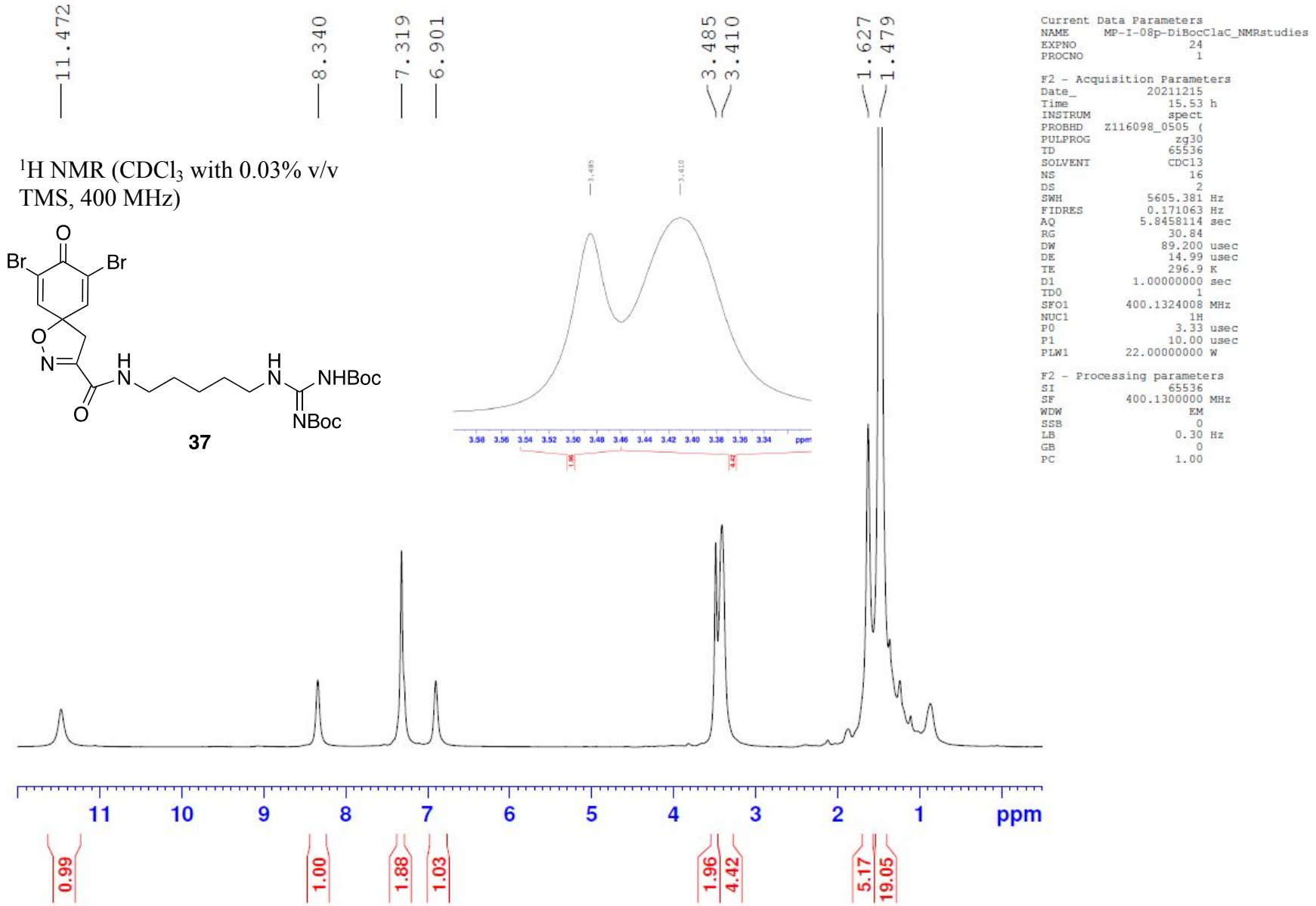

Figure S62. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 100 mg of known compound (**36**) in 0.6 mL of untreated $CDCl_3$, T0.

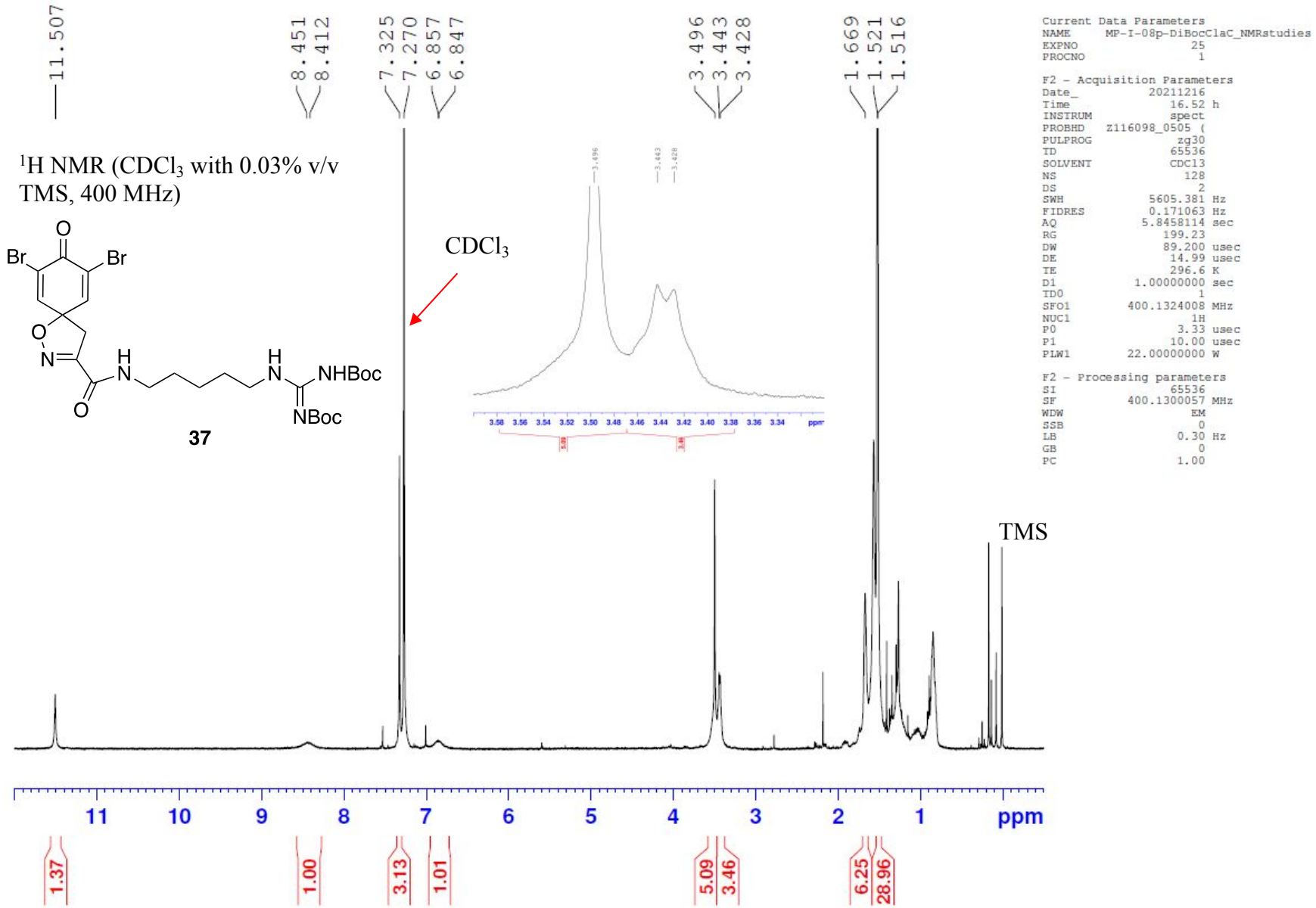

Figure S63. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 0.8 mg of known compound (**36**) in 0.6 mL of untreated $CDCl_3$, T1.

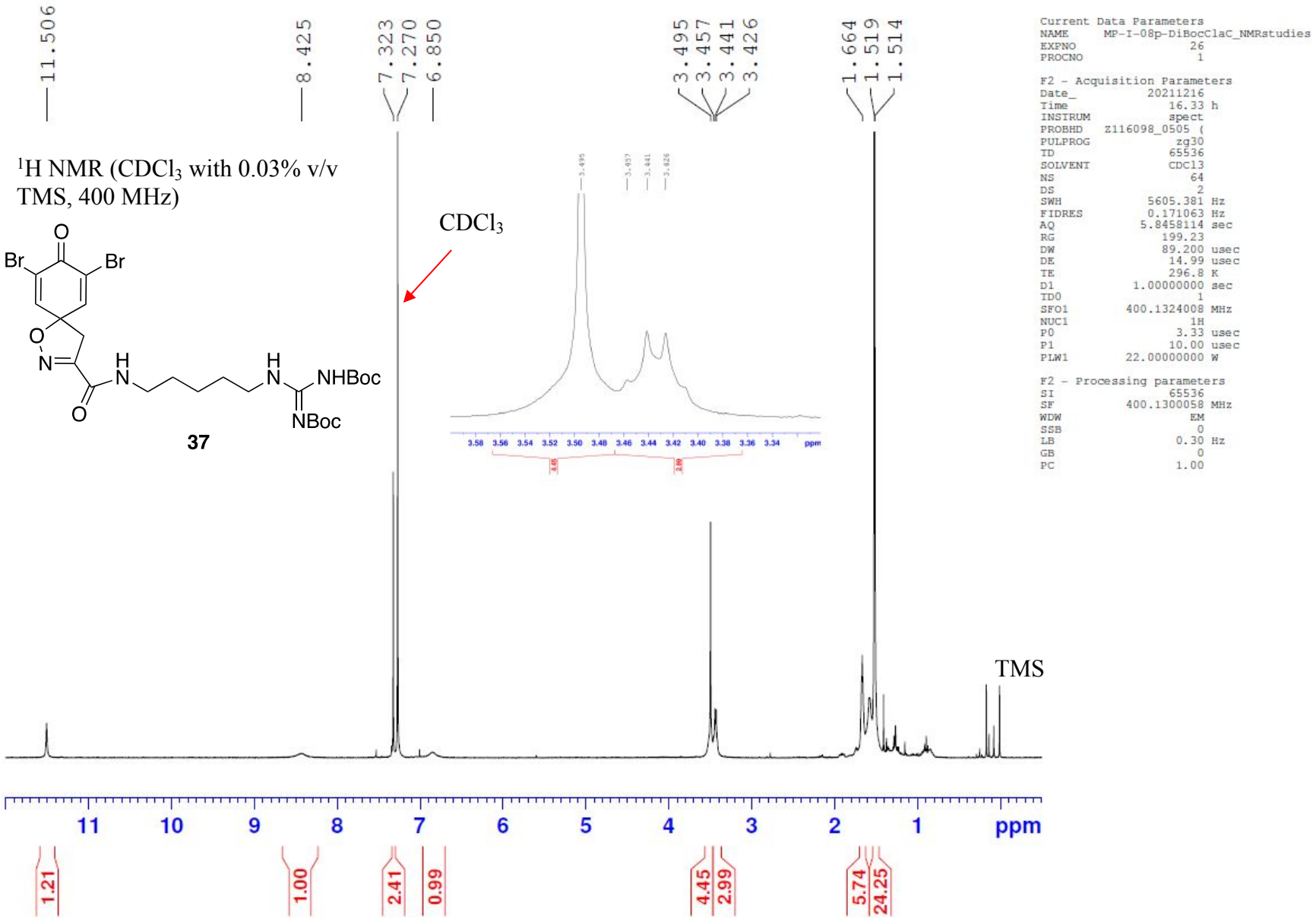

Figure S64. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 1.6 mg of known compound (**36**) in 0.6 mL of untreated $CDCl_3$, T1.

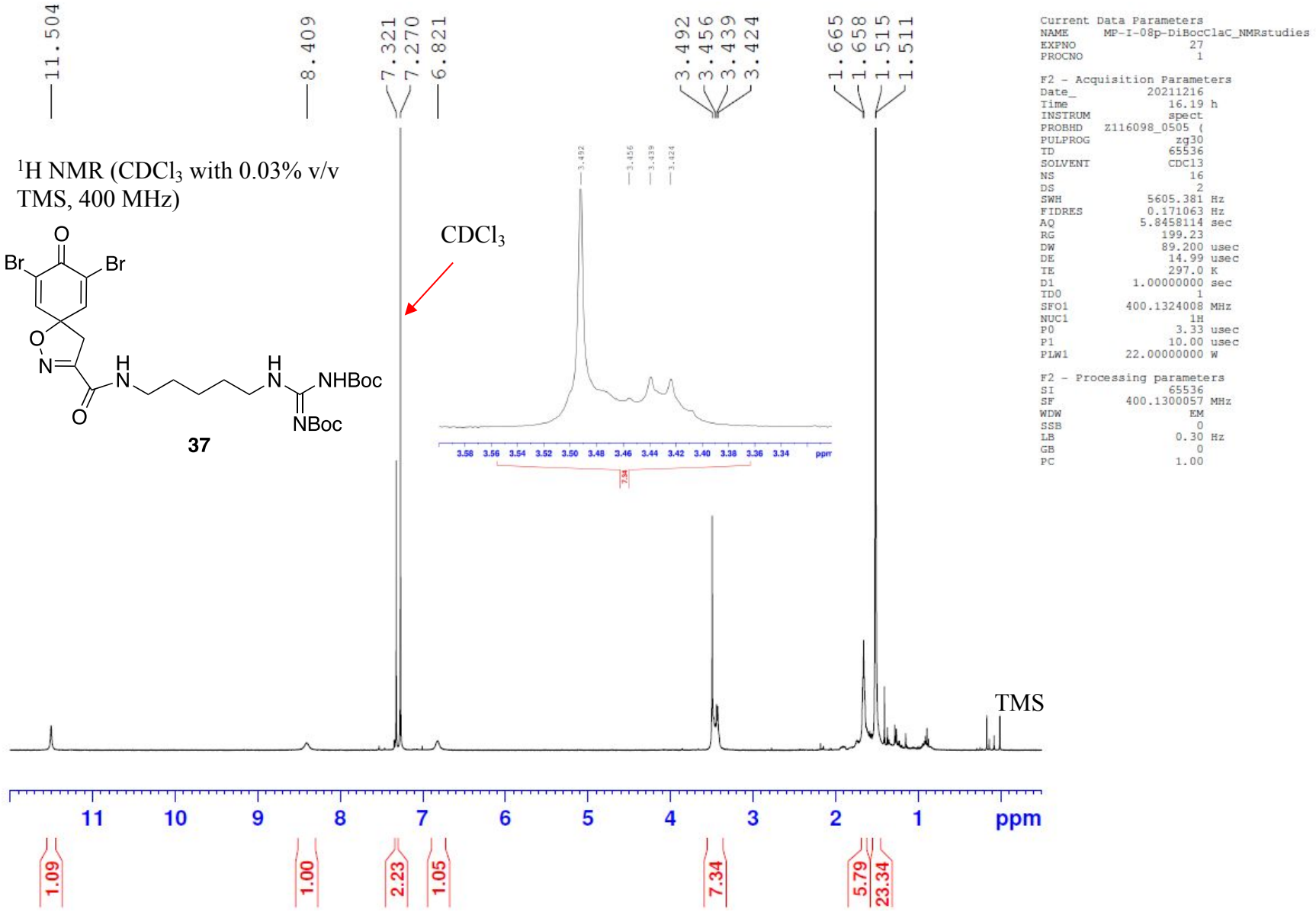

Figure S65. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 3.1 mg of known compound (**36**) in 0.6 mL of untreated $CDCl_3$, T1.

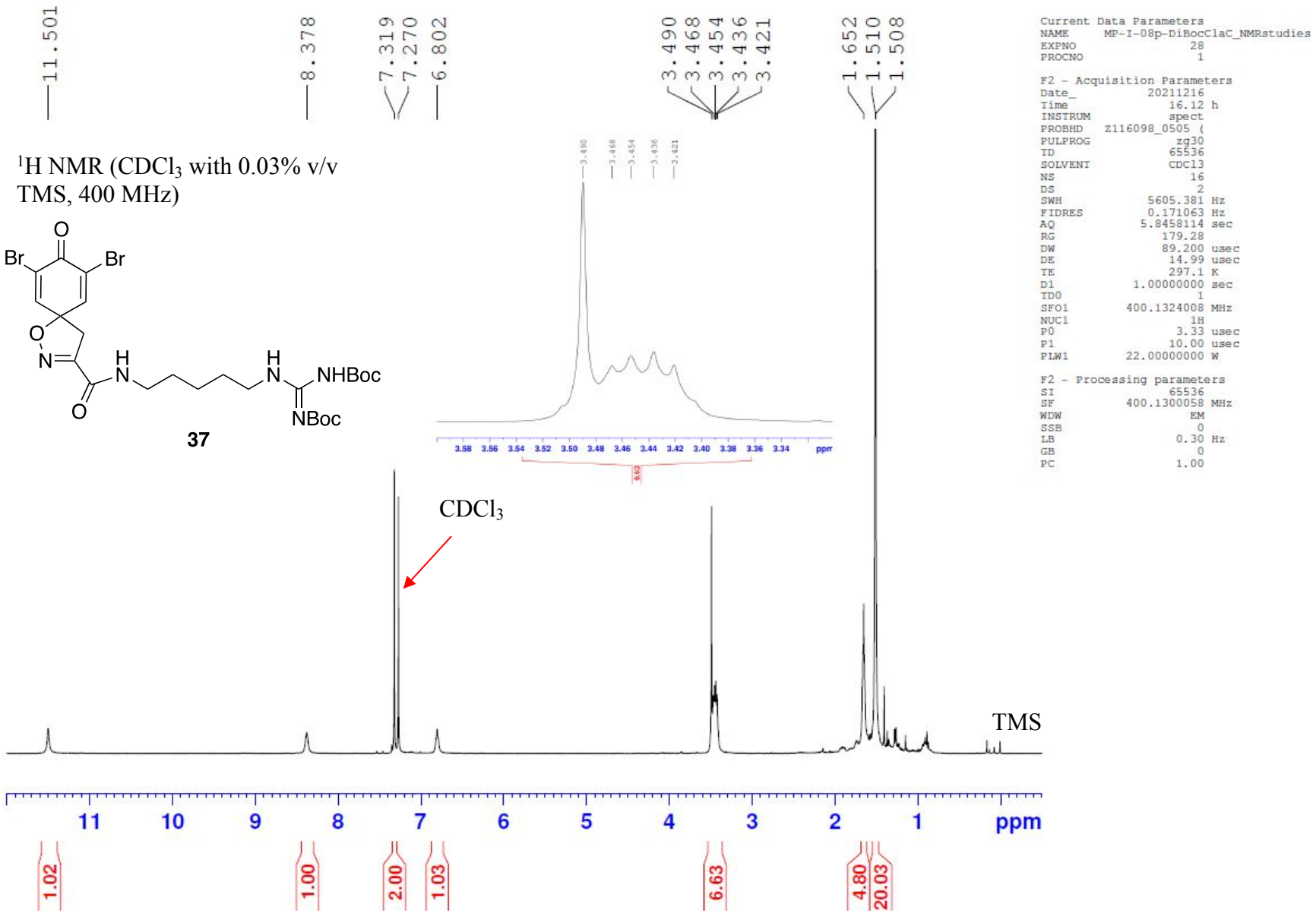

Figure S66. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 6.2 mg of known compound (**36**) in 0.6 mL of untreated $CDCl_3$, T1.

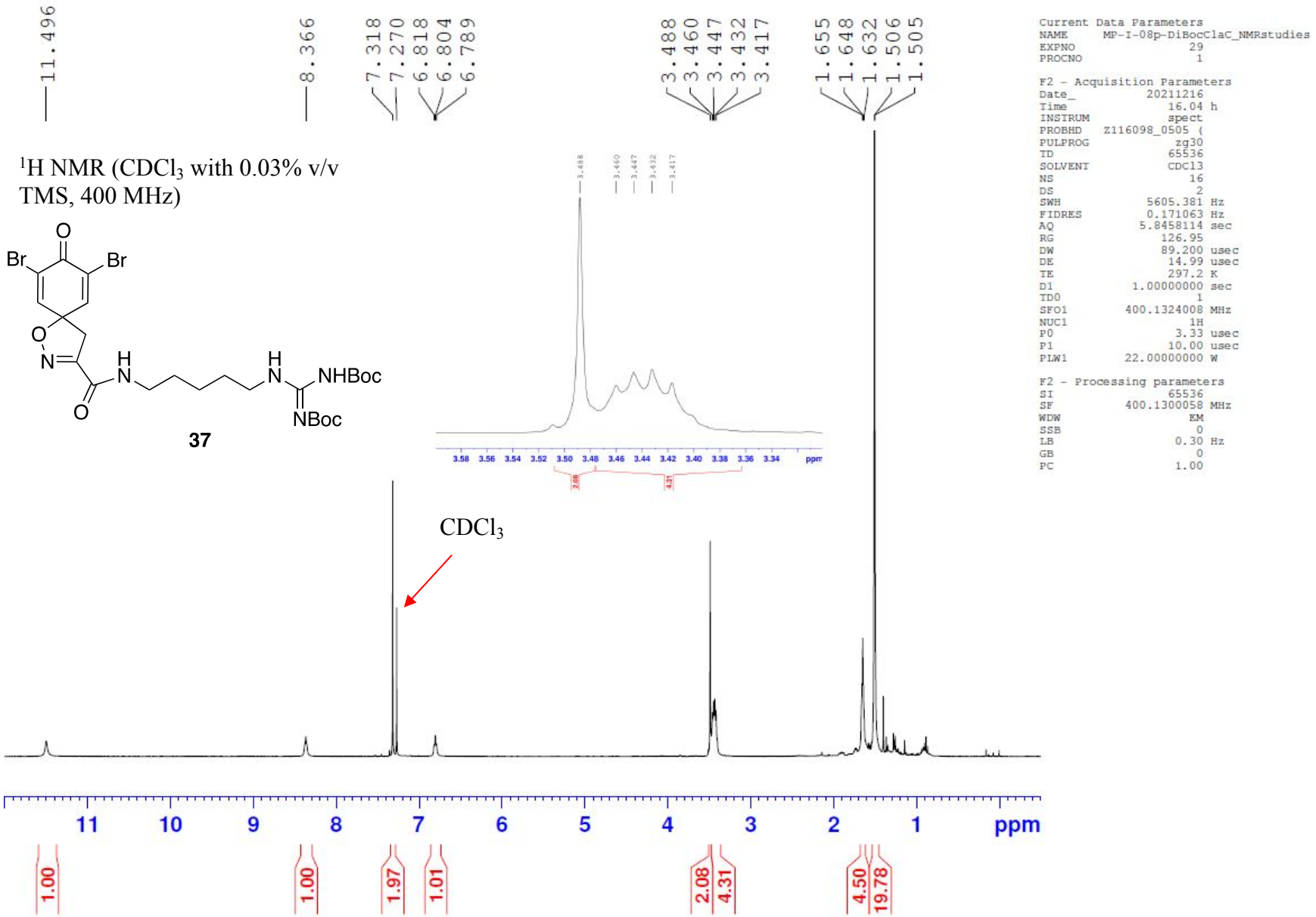

Figure S67. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 12.5 mg of known compound (**36**) in 0.6 mL of untreated $CDCl_3$, T1.

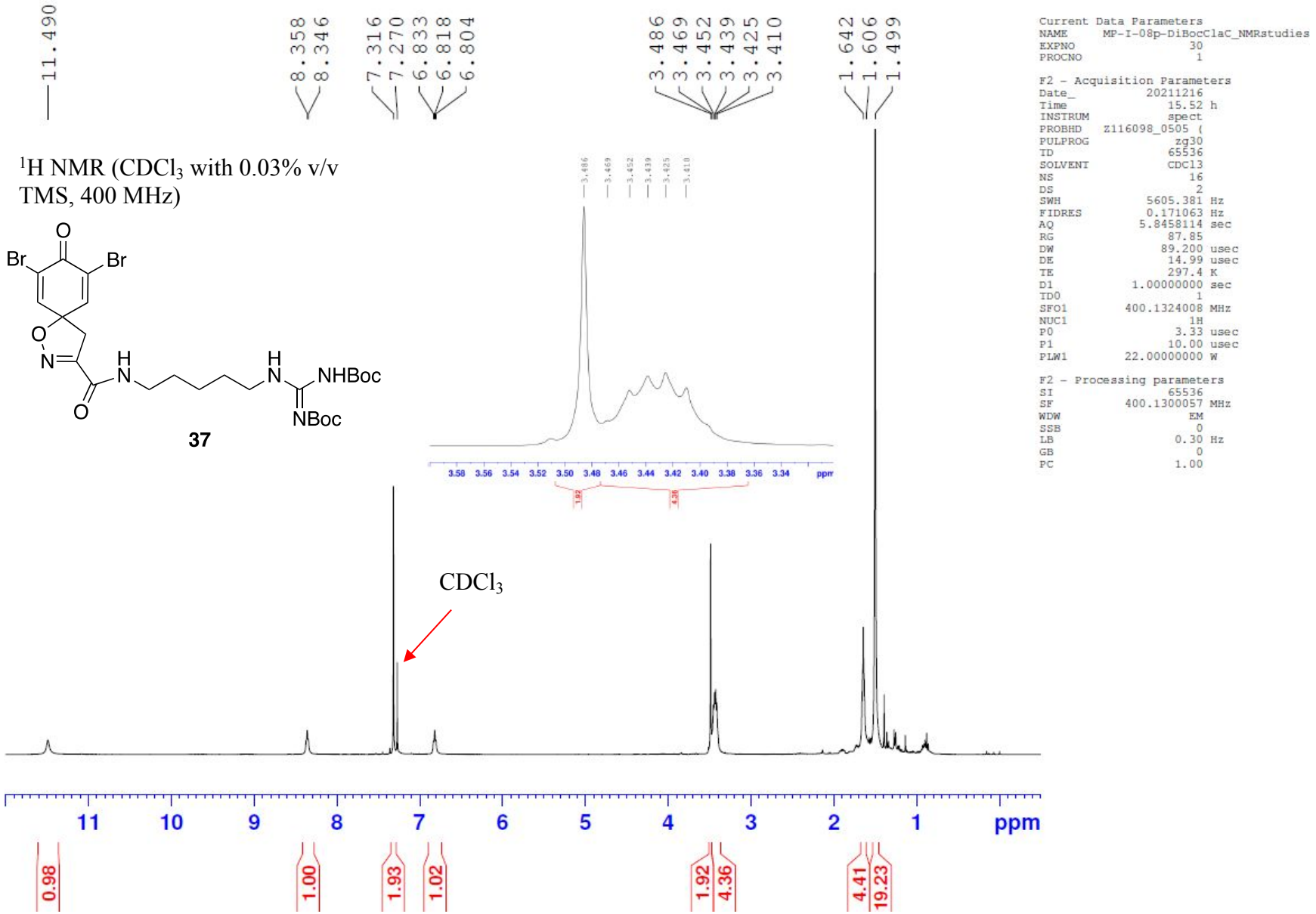

Figure S68. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 25 mg of known compound (**36**) in 0.6 mL of untreated $CDCl_3$, T1.

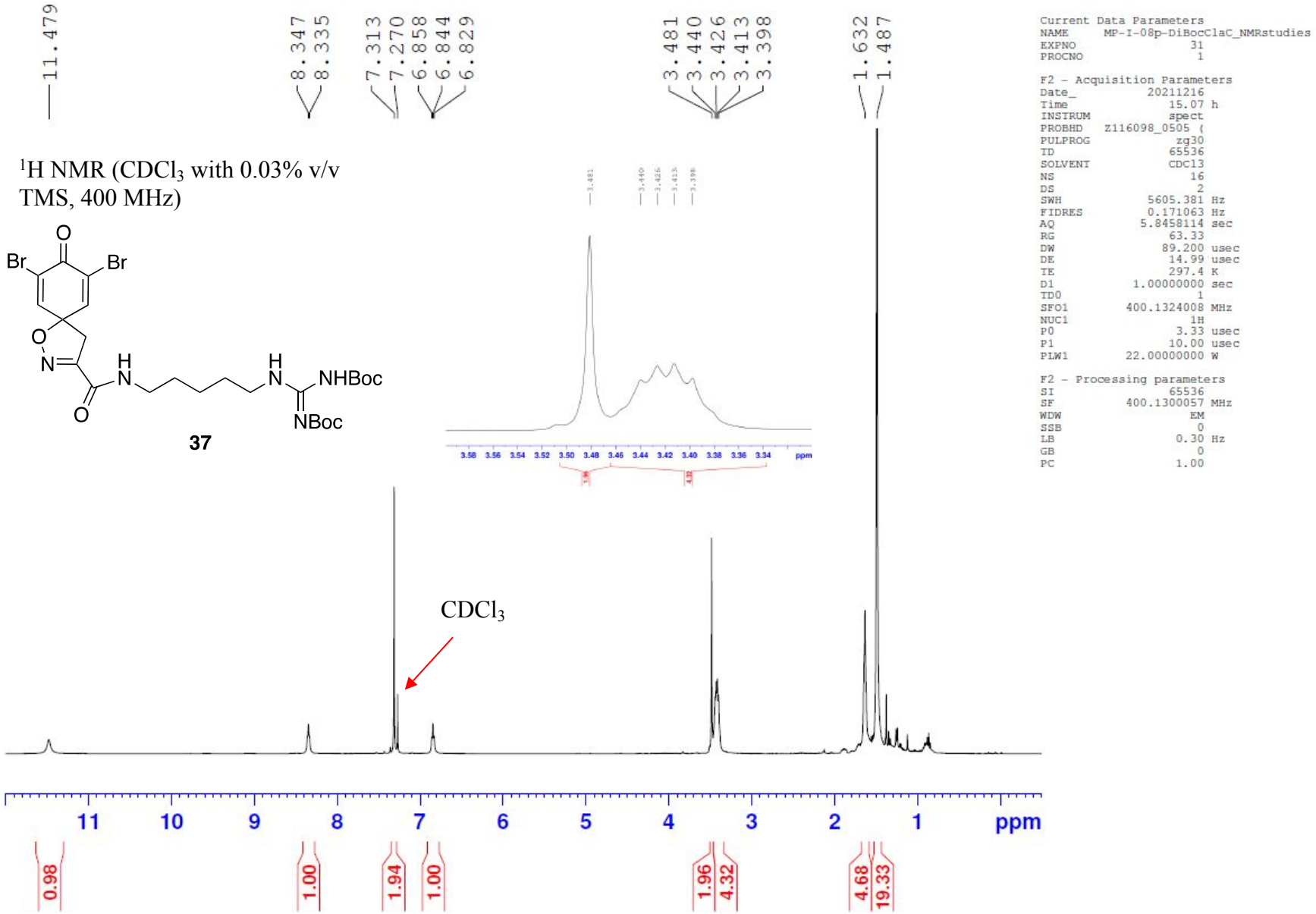

Figure S69. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 50 mg of known compound (**36**) in 0.6 mL of untreated $CDCl_3$, T1.

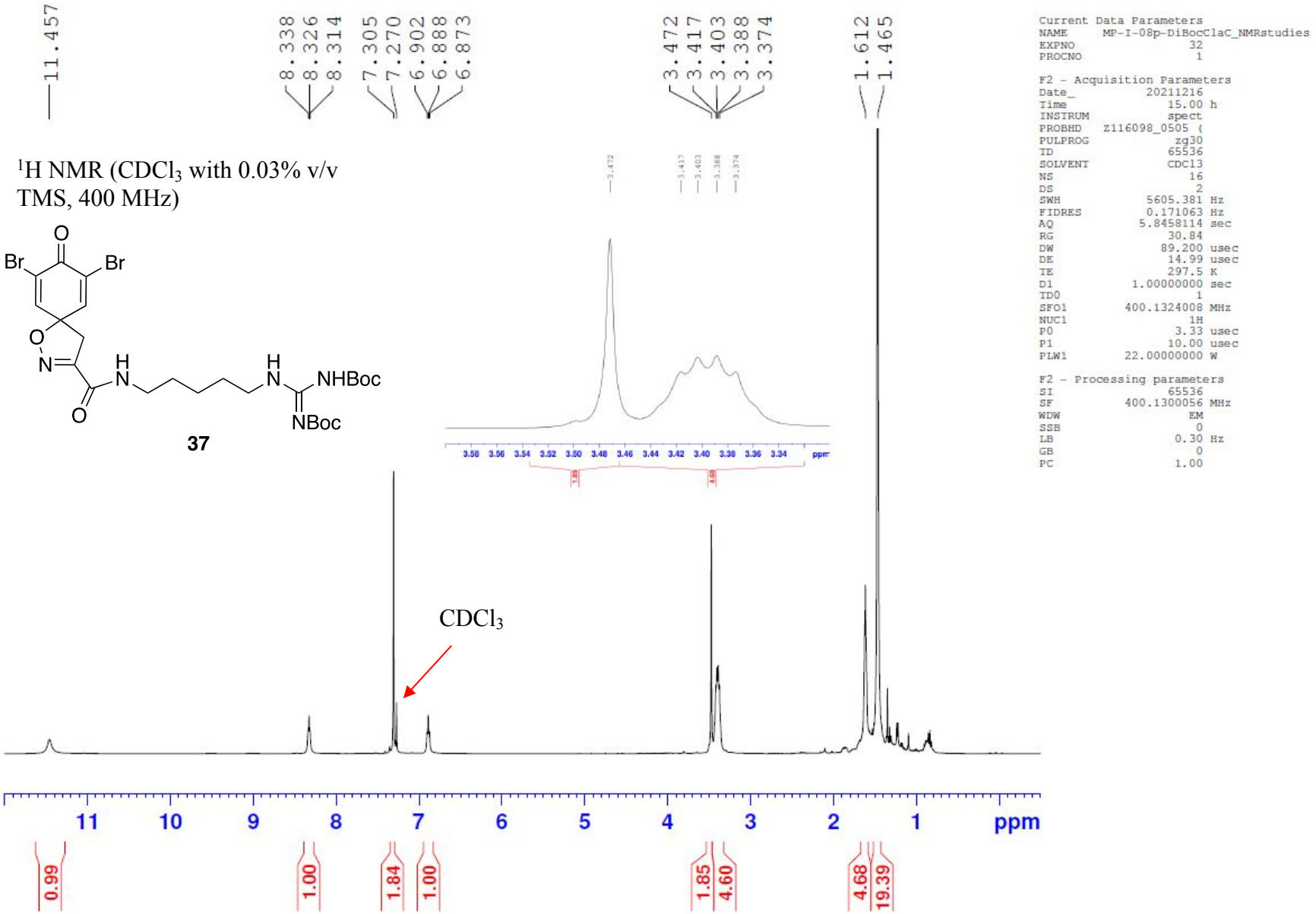

Figure S70. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of 100 mg of known compound (**36**) in 0.6 mL of untreated $CDCl_3$, T1.

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(1) Buchanan, M. S.; Carroll, A. R.; Wessling, D.; Jobling, M.; Avery, V. M.; Davis, R. A.; Feng, Y.; Xue, Y.; Öster, L.; Fex, T.; Deinum, J.; Hooper, J. N. A.; Quinn, R. J. Clavatadine A, A Natural Product with Selective Recognition and Irreversible Inhibition of Factor XIa. *J. Med. Chem.* **2008**, *51*, 3583–3587.

(2) Guzman, A. L.; Hoye, T. R. TMS Is Superior to Residual $CHCl_3$ for Use as the Internal Reference for Routine ^1H NMR Spectra Recorded in $CDCl_3$. *J. Org. Chem.* **2022**, *87*, 905–909.